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INTERNATIONAL SOCIETY OF GYNECOLOGICAL ENDOCRINOLOGY

GREM

Gynecological and Reproductive Endocrinology & Metabolism

SUPPLEMENT 1

Book of abstracts of Gynecological Endocrinology the 19th World Congress

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VOLUME 1 · SUPPLEMENT 1 · 2020

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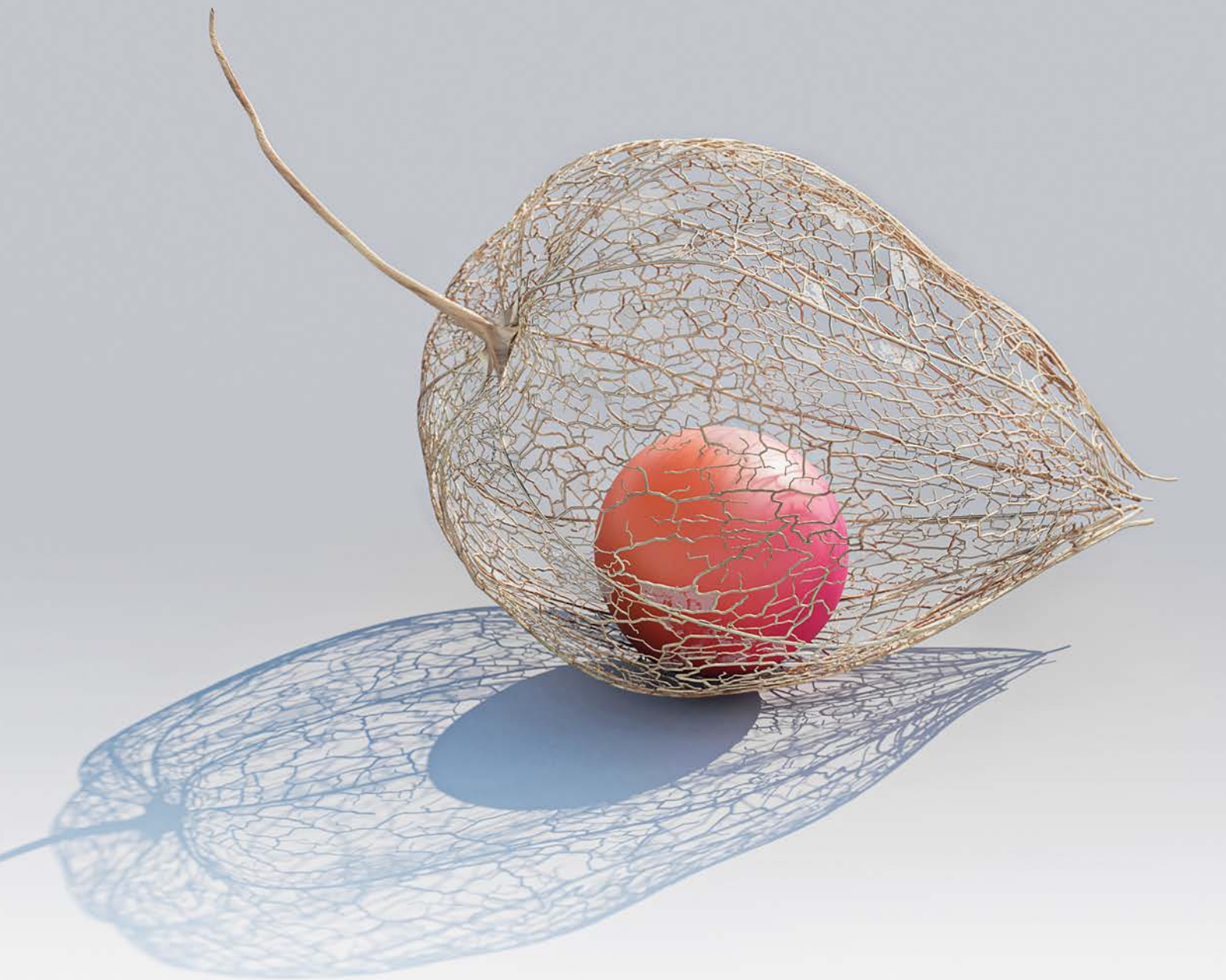

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VOLUME 1 • SUPPLEMENT 1 • 2020

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BTpress
www.btcongress.com

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Production Office
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00139 Rome, Italy
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The Journal

Gynecological and Reproductive Endocrinology and Metabolism, an Open-Access Journal of the ISGE, will publish Editorials, Statements, Position Papers, Systematic Reviews, Meta-analysis, Short-Reviews, Original Articles and Case Reports on the research area of the fields of Gynecology, Obstetrics, Reproduction, Feto-Maternal Medicine, Basic Science, Pharmacology, Epidemiology, Metabolism, Oncology, Neuro-Endocrinology Psycho-Somatic Medicine,Sexology, Female Aging, Ethics, Quality of Life and any other aspects of Gynecological and Reproductive Endocrinology and Metabolism. In particular articles related to Endocrine Therapies in women, Puberty, Adolescent Gynecology, Contraception, Fertility, Polycystic Ovary, Endometriosis, Assisted Reproduction, Abortion, Eclampsia, Gestational Diabetes Mellitus, Premature Labor, Breast Feeding, Premature Ovarian Insufficiency, Menopause, Female Sexual Dysfunction, Osteoporosis, GSM/VVA and any other topics related to Gynecological and Reproductive Endocrinology and Metabolism will be welcome.

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GREM is published quarterly in March, June, September and December by International Society of Gynecological Endocrinology

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EDITORIAL

Dear Friends

For all Executive Committee of the International Society of Gynecological Endocrinology is a pleasure to introduce the Abstract Book of the 19th World Congress of Gynecological Endocrinology (On Line Congress 2-5 December 2020, available until 15 April 2012) as Supplementum n. 1 of our New Open-Access Journal: GREM – Gynecological and Reproductive Endocrinology and Metabolism.

This represents a further effort of ISGE to promote investigations and education in Gynecological Endocrinology. GREM is the demonstration of the vitality and worldwide engagement of ISGE to stimulate the upgrading of Gynecologists and Obstetricians in Gynecological and Reproductive Endocrinology and Metabolism.

The New Open-access GREM, edited by ISGE in collaboration with BTpress and Medimay will publish all kind of papers: Editorials, Statements, Position Papers, Reviews, Meta-analyses, Original Articles and Case Reports covering all areas of Gynecological, Obstetrical and Reproductive Endocrinology, and Metabolism.

The 19th World Congress Abstract Book, as Supplement n. 1 of GREM, includes all received abstracts of Key Lectures, Symposia, Meet the Experts, Scientific Societies Symposia, 249 Oral presentations, 350 Posters and the abstracts of the sessions organized by our Sponsors.

This volume contains also the abstracts of the Lectures of the ISGE Scholarship Special Course for trainees and Post-Doc who participated in our Scholarship Program.

We invite all of you to go to the third cover page of this book and to accept our invitation: GREM is looking for your Manuscript!

I would like to express our gratitude to Peter Chedraui as Editor in Chief since January 2020 of our first journal: Gynecological Endocrinology, who started in March 1987, edited by Taylor and Francis, successfully growing as quality and number of papers received and published.

With this in mind, I wish for all of you to enjoy the on-line participation to the19th World Congress of Gynecological Endocrinology to enrich your culture and your knowledge in this fantastic discipline who covers areas of fundamental importance for women health and quality of life.

Andrea R. Genazzani
President of ISGE

Key Lectures

(KL02) The human yolk sac, perhaps the most important transient organ

The human yolk sac, perhaps the most important transient organ

Frederick Naftolin (US)
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The human embryo-fetus develops several transient organs. These include the placenta, the fetal adrenal reticular zone and the yolk sac. While the first two are well-documented and studied, the yolk sac is generally only thought of as the source of endodermal mesenchymal precursor cells. Its early origins in the blastula are unstudied except for anatomic specimens that are characterized in a comparative biology context. Yet, the direct inclusion by the pincer-like action of the developing amniotic sac in the body of the embryo of the dorsal part of the (primary) yolk sac includes much of the precursors of the gut, blood and vessels and other systems in the corpus of the developing embryo-fetus. More such stem elements enter via the vitelline vessels before the (secondary) yolk sac is eclipsed and shunted off to the edges of the developing chorion-amnion interface. With the availability of high-resolution ultrasound, there has been a resurgence of studies on the morphology of the secondary yolk sac, primarily as a harbinger of the health of the developing embryo-fetus.

Animal studies have shown the importance of the yolk sac in development. For example, comparatively small changes in glucose levels result in the increase in fetal anomalies that plagued the offspring of uncontrolled diabetics. Tight glucose control has reduced the rate of anomalies of diabetic pregnancies to less than that of normal pregnancies.

With the availability of cells removed from embryos *in vitro* and dated products of conception from failed *in vitro* fertilization cases, the opportunity to properly study the yolk sac has arisen. Scientific study of this important transient organ should be a high priority in the coming decade.

(KL06) Translational research with thyroid hormone in the placenta

Translational research with thyroid hormone in the placenta

Takeshi Maruo (JP)
Kobe Children's Hospital

Clinically it is known that hypothyroidism is one of the endocrine factors for early pregnancy loss. Corpus luteum is the prime source of P4 production in very early pregnancy, and placenta takes over the corpus luteum function at 6- week of pregnancy. The adequate functional shift from corpus luteum to placenta is indispensable for early pregnancy maintenance. To elucidate the molecular mechanism by which thyroid hormone takes a vital role in maintaining early pregnancy, the effects of thyroid hormone on granulosa cell luteinization and trophoblast function were first investigated *in vitro*. Treatment with 10-8M T3 enhanced granulosa cell luteinization and trophoblast endocrine function in producing P4 and hCG. Treatment with either higher or lower doses of T3 gave attenuated effects.

Then, to determine the effects of T3 on apoptosis and invasive potential of extravillous trophoblasts (EVTs), trophoblasts differentiating into EVTs was isolated by enzymatic digestion of anchoring chorionic villi. The placental cells attached to fibronectin (FN)-precoated dishes were positive for specific EVT markers. The isolated EVTs expressed c-erbA1 transcript, indicating the presence of T3 receptor. In cultured EVTs, treatment with 10-8M T3 decreased apoptosis through inhibiting Fas/Fas ligand, caspase-3 and PARP (poly (ADP-ribose) polymerase). Trearment with 10-8M T3, on the other hand, increased cell adhesion molecules including MMPs, fetal FN and integrin$\alpha 5\beta 1$, and VEGF in cultured EVTs. Matrigel invasion assay revealed that 10-8M T3 increased cell projections of EVTs which penetrated the filter pores. These findings suggest that the optimal dose of T3 promotes EVT invasion to the decidua by decreasing apoptosis and by increasing VEGF, MMPs and integrin in EVTs. This explains in part the molecular mechanism for the vital role of thyroid hormone in early pregnancy maintenance.

Actually, meta-analysis conducted by Rao et al. (Hum Reprod Updates 2019) confirmed that T4 supplementation reduces the risk of pregnancy loss in women with clinical/subclinical hypothyroidism. International practice guideline has recommended that early pregnancy serum TSH level should be lower than 2.5mU/l, and that once hypothyroidism is identified by increased TSH, T4 replacement is crucial for the prevention of early pregnancy loss. The dose of T4 supplementation should be adjusted on the basis of free T4 in the high normal and TSH in the low normal area.

(KL08) Emerging health issues for women in the reproductive years- findings from the Grollo-Ruzenne Study

Emerging health issues for women in the reproductive years- findings from the Grollo-Ruzenne study

Susan Davis (AU), Marina Skiba (AU), Rakibul Islam (AU), Jia Zheng (AU), Robin Bell (AU)
Monash University

The Grollo-Ruzzene Foundation Younger Women's Health Study is a cross-sectional study of a representative sample of 6986 Australian women, aged 18-39 years, living in the eastern Australian states of Victoria, New South Wales, and Queensland. The study was specifically designed (and powered) to achieve a better understanding of polycystic ovarian syndrome (PCOS). Despite the reported high frequency of this condition, the diagnostic criteria are primarily based on expert opinion and lack standardisation, resulting in uncertainty surrounding the diagnosis. To achieve this outcome, it was essential to recruit a non healthcare-seeking, community based ,representative sample. Recruitment, by predominantly electronic means, achieved a study sample with a profile representative of age-matched Australian women and, by comparison with national census data, external validity of the study sample was established (Skiba et al ANZJPH 2019). This approach has allowed us to take a "snap shot" of the health and wellbeing of young Australian women. In sub-studies we have documented sex steroids measured by LC/MS-MS and ovarian morphology by ultrasound. The findings to date, for the entire cohort, include the prevalence of sexual difficulties and sexual difficulties associated distress (Zheng et al Fertil Steril 2020), the use of contraceptives (Skiba et al ANZJO&G 2019), prevalence of depression and use of anti-depressants, modified Ferriman-Gallwey score distribution, mF-G associations with and sex steroids measured by LC/MS-MS (Skiba et al JCEM 2020). In the sub-studies we have documented sex steroids by age (Skiba et al JCEM 2019), the prevalence and risk factors for iron insufficiency, sex steroid associations with disorders of sexual function sexual, the distribution of ovarian morphology in young non-healthcare seeking women and estimations of PCOS prevalence.

(KL10) Sex, gender, and the brain

Sex, gender, and the brain

Walter Rocca (US)
Mayo Clinic

Objective

To discuss the effects of variables related to sex and gender on the brain, with focus on late life and aging. Dementia and Alzheimer's disease (AD) are used as examples.

Methods

I will discuss: 1) Definitions and mechanisms related to sex; 2) definitions and mechanisms related to gender; and 3) differences in risk and protective factors for dementia and AD.

Results

Sex is a biological variable that involves chromosomes, gonads, hormones, and reproduction (e.g., number of pregnancies, breast feeding). Gender is a social and cultural variable that involves subjective components (e.g., gender identity) and societal and cultural components (e.g., legal rights and social roles of men and women). Sex and gender variables have major effects on dementia: on frequency and distribution, risk and protective factors, clinical manifestations, response to treatment, and long-term prognosis. Risk and protective factors may differ between men and women in frequency (e.g., education), magnitude of the effect (e.g., APOE genotype), or both (e.g., head trauma). Some risk or protective factors are restricted to one sex (e.g., bilateral oophorectomy).

Conclusions

Sex and gender related variables affect the brain throughout life. The effects on late life and aging are particularly important to understand the common age-related chronic conditions such as dementia and Alzheimer's disease.

(KL11) Dreams and Gender

Dreams and gender

Zipora Dolev (IL)
Tel Aviv University

From the dawn of history, people were engaged with their dreams and gave them mystical meanings. One of the richest sources of dreams from the ancient world is, of course, the Bible.
To this day, scientists are trying to decode the secrets of dreams, their role in our lives, their biological function, and the mechanism that creates them.
The sleeping stage in which we dream is he REM stage which has a critical role in the correct activity of the brain.
Gender medicine, a field still in its infancy in the world at large, and is dedicated
to the study of the different frequencies of diseases and the differences in the way the
same disease manifests itself in each gender.
The differences between men and women are reflected both in our biology and in our dreams. It is also very clear that there is a link between hormonal changes in a woman's life and her dreams. Just as hormones affect our mental states as women, they certainly affect the content of our dreams.
I will discuss the difference between the content of women's dreams and men's dreams.
I will discuss the content of women's dreams in relation to her hormonal changes through life.

(KL12) GnRHa triggering of final oocyte maturation: optimizing the luteal phase

GnRHa triggering of final oocyte maturation: optimizing the luteal phase

Johnny Awwad (LB)
American University of Beirut Medical Center

The use of gonadotropin-releasing hormone agonist (GnRHa) for the final induction of oocyte maturation in *in vitro* fertilization (IVF) cycles has gained momentum recently over the use of human chorionic gonadotropin (hCG) in women at high risk for ovarian hyperstimulation syndrome (OHSS). Because of the shorter duration of the GnRHa-induced LH surge, earlier demise of the corpus luteum has been observed yielding a significant reduction in the risk for OHSS at the peril of adversely altering embryo implantation. For these reasons, the effectiveness of GnRHa triggering has been put to scrutiny, and the quest for the most optimal luteal phase support (LPS) for this type of cycle has yet to be resolved. Earlier studies using this triggering approach were not encouraging because of reportedly high pregnancy losses and low pregnancy rates. The adoption of a GnRH agonist trigger protocol with segmentation of the IVF cycle has therefore been proposed with the aim of restoring reproductive success without compromising patient safety. When a fresh embryo transfer is planned, however, alternative strategies may be utilized, namely, the prevention of luteal demise by a low-dose hCG rescue or the use of intensive supplementation of the luteal phase.

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References: 1. Amy JJ. Femoston: effects on bone and quality-of-life. *Eur Menopause J* 1995;2(4), (Suppl):16–22. 2. Company Core Data Sheet, Estradiol/Dydrogesterone, Abbott Laboratories, 15 January 2016.

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Symposia

(SYMP02) Neuroendocrinology/FHA

Kisspeptin role in reproductive functions and dysfunctions

Blazej Meczekalski (PL)
PoznanUniversity of Medical Sciences, Poznan, Poland

Kisspeptin is regarded as the potential main player in the GnRH regulation. Kisspeptin was identified as a peptide encoded by KISS1 gen in 1996.
The main site of kisspeptin secretion is hypothalamus and more precisely arcuate nucleus and preoptic region of hypothalamus. Additionally is secreted in small amounts by ovary, intestine, and placenta. It plays an essential role in regulation of GnRH secretion. Kisspeptin is responsible for direct positive influence on GnRH synthesis and release. Very important kisspeptin role is reffered to physiology of hypothalamic-pituitary-ovarian axi, implantation, early pregnancy and puberty onset. It presents also important role in regulation of energy balance and metabolism.
Kisspeptin can also play an inmportant role in such reproductive dysfunction like functional hypothalamic amenorrhea (FHA), polycystic ovary syndrome (PCOS), miscariagge. Ther are also approaches to use kisspeptin as a marker of infertility and treatment tool for management different reproductive disorders.

(SYMP03) PCOS: the beginning

Brain phenotype in PCOS – androgens, anovulation, and gender

Sarah Berga (US)
University of Utah

Fundamental questions related to the pathogenesis of polycystic ovary syndrome (PCOS) are 1) whether the brains of women with PCOS are partially androgenized and 2) if so, to delineate the reproductive and behavioral consequences thereof. One is the central paradoxes of PCOS is that women with PCOS have more oocytes than age-matched eumenorrheic women (EW) yet they nonetheless experience chronic anovulation. The chronic anovulation has been attributed to FSH levels that are insufficient to initiate and/or sustain folliculogenesis. Insufficient FSH, in turn, has been attributed to increased GnRH drive, particularly increased GnRH pulse frequency, which not only decreases FSH but also increases LH. Increased LH drives the ovarian thecal cells to overproduce androgens. The AMH from an increased oocyte pool may also contribute to increased GnRH drive. We have shown that women with PCOS show an increase in cerebrospinal fluid (CSF) levels of GABA, testosterone, and estradiol (E2), any or all of which may independently and synergistically androgenize the brain. E2 is a masculinizing hormone and exerts multiple region-specific effects via distinct cellular mechanisms. Studies show that Women with PCOS more often viewed themselves as sexually undifferentiated compared with controls (32 vs 7%), were less likely to identify with a female gender scheme (18 vs 33%), and more likely to view themselves as androgynous (50 vs 41%) (Acta Obstet Gynecol Scand 2012). In addition, women with PCOS reported lower happiness scores, were less gender conforming, and trended toward bisexual orientation (Ann Hum Biol 2008). Using Swedish national registers, women with PCOS (24,385), full siblings (25,921), and matched individuals compared for psychiatric disorders, PCOS had increased risk for bulimia, schizophrenia, bipolar disorder, depressive and anxiety disorders, personality disorders, and autism spectrum disorders (Psychoneuroendocrinology 2016). Based on the above, it is important to view PCOS as a condition with both a reproductive and a gender phenotype, both of which may reflect increased exposure of the brain to androgens and estradiol.

(SYMP04) PCOS

Polycystic ovary and it's endocrine challenges

Amala Nazareth (AE)
Prime Healthcare Group Dubai UAE

Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrinopathy in women and the most common cause of anovulatory infertility. Patients with PCOS have clinical and biochemical features consistent with the ultrasound diagnosis and they are likely to face the problems of hyperandrogenism, subfertility and recurrent miscarriage. The aim of the presentation is to summarize our present knowledge on the hormonal background of this very prevalent syndrome and to give some clinical examples how the present knowledge can be applied to treat PCOS patients according to their current problem, such as menstrual cycle disorder, hirsutism, infertility or to prevent late consequences as diabetes mellitus. The etiology and pathogenesis of PCOS is still a matter of controversies, but it is apparent that inappropriate gonadotropin secretion, obesity, hyperinsulinism and insulin resistance are the major determining factors in the development of ovarian hyperandrogenism an chronic anovulation. Reversal of insulin resistance in PCOS constitutes the fundamental goal in the management of hyperandrogenic anovulatory infertility and in the prevention of long-term consequences.

(SYMP04) PCOS

Treatments of metabolic syndrome in PCOS

Massimo Stomati (IT), Raffaele Tinelli (IT), Andrea Tinelli (IT)

[Stomati] Dept. of Obstetrics and Gynecology, "D. Camberlingo" Hospital, Francavilla Fontana, ASL Brindisi, [Tinelli] Dept. of Obstetrics and Gynecology, "Valle D'Itria" Hospital, Martina Franca, ASL Taranto, Italy, [Tinelli] Dept. of Obstetrics and Gynecology

Women with polycystic ovary syndrome (PCOS) present a broad spectrum of phenotypes. Insulin resistance is not universal in PCOS. However, certain phenotypes are associated with insulin resistance and an increased long-term risk of developing diabetes, metabolic syndrome (MBS), and cardiovascular disease, which are compounded by obesity. The ideal therapy for PCOS with MBS is one that restore normal hypothalamic pituitary function, with return of normal steroidogenesis at the level of the ovary, with normalization of androgen excess and insulin resistance. Ultimately, the normalization of the hypothalamic pituitary ovarian adrenal axis would lead to a normalization of the attributable component of MBS, obesity, insulin resistance, lipid profile, liver dysfunction and amelioration of cardiovascular risk. No single therapeutic has achieved this goal to date. Diet, caloric restriction and exercise are strictly recommended to all women affected from PCOS and MBS. First-line therapeutics, such as OCPs, antiandrogens and insulin sensitizers, have resulted in changes in level of the hypothalamus–pituitary–ovarian axis (OCPs), decreased androgens (OCPs and antiandrogens) and improved glucose metabolism. Metformin has addressed several of these pathways but has fallen particularly in the reduction of androgen excess in obese individuals with PCOS. Furthermore, women with PCOS-MBS who desire fertility pose an additional challenge due to contraindications and safety in pregnancy. Despite these limitations, there are several emerging therapeutics for PCOS with MBS. Though most of these emerging therapeutics do not seem to address all pathways, addressing key factors of MBS may succeed in diminishing long-term cardiovascular risk. D-chiro-inositol, a newer insulin sensitizing agent, may ultimately prove to help women with PCOS and MBS. Vitamin D, a key factor in calcium homeostasis and bone metabolism, has been evaluated with note that normal levels of vitamin D are associated with normal insulin metabolism. Other emerging therapeutics that may act at the level of the hypothalamus and pituitary are important to consider. Among these, Naltrexone, an opioid antagonist acting through increase of beta-endorphins and sympathetic nervous system activity, has been shown to normalize response to GnRH stimulation in women with PCOS and improve insulin sensitivity. More studies are required regarding the model of these new treatments and to prove their efficacy.

(SYMP05) Androgens

Androgen substitution - risks and benefits

Martin Birkhaeuser (CH)
University of Berne, Switzerland

The Global Consensus Position Statement on the Use of Testosterone Therapy for Women concluded that the only evidence-based indication for testosterone (T) therapy in physiologic dose is for the treatment of HSDD.

Benefits

T exerts a beneficial effect on sexual function. There are insufficient data to support the use of T for the treatment or the prevention of any other symptom or clinical condition. However, in premenopausal women, limited data show that T administration putting the serum levels in the upper physiological range increase muscle strength and performance in female runners.

Risks

T administration in physiologic dose is not associated with serious adverse events. However, the safety of long-term T therapy has not been established. Women "at-risk" have been excluded from the study populations analyzed in the trials published until now.
Systemic T therapy for postmenopausal women is associated with mild increases in acne and body/facial hair growth in some women, but not with alopecia, clitoromegaly or voice change. Non-oral T therapy has not been associated with increases in blood pressure, blood glucose or HbA1c levels. In contrast to non-oral T therapy, oral T administration is associated with adverse lipid profiles with negative effects on HDL-cholesterol and LDL-cholesterol levels and should not be used.
A non-significant trend for an increased risk of deep venous thrombosis (VTE) has been seen with T therapy, however the role of concurrent estrogen therapy in possible VTE risk cannot be excluded.
Because of limited data regarding the long-term effect of physiologic doses of T in postmenopausal women, no recommendations can be formulated beyond 24 months of treatment concerning cardiovascular health and long-term breast cancer risk.

(SYMP05) Androgens

The global position statement on androgens in women - where to from here

Susan Davis (AU)
Monash University

In September 2019 the International Menopause Society, and 10 other international medical societies published the first Global Consensus Position Statement on the use of testosterone for women. The Statement was by consensus of a diverse team of leading experts nominated by their organisations. It follows decades of debate regarding testosterone therapy for women and, for the first time, provides agreement among experts and medical societies about why, when and how testosterone may be prescribed for women. The Task Force made recommendations about measurement of testosterone in women and best practice guidance for the diagnosis of sexual dysfunction.
The position statement has far reaching global consequences. It not only demonstrates that a trial of testosterone therapy is appropriate for women with Hypoactive Sexual Desire Dysfunction (HSDD) but very emphatically states that, at present, the available evidence does not support the use of testosterone for any other symptoms or medical conditions. It also clearly advises that when testosterone therapy is given, the resultant blood levels should not be above those seen in healthy young women. This allows for women with HSDD to be offered treatment and simultaneously protect women from receiving inappropriate testosterone therapy that is being promoted by some practitioners.

(SYMP06) Insulin resistance/metabolic syndrome

Obesity during mid-life: why does it impact cardiovascular risk?

Peter Chedraui (EC)
Instituto de Investigación e Innovación en Salud integral, Universidad Católica de Santiago de Guayaquil

During the female menopausal transition there is a gradual decrease in the secretion of ovarian estrogens, which has been correlated to female bio, psycho- and social changes. Estrogens play an important role in maintaining appropriate functioning of many systems and organs. As women age, and as a direct or indirect consequence of this progressive estrogenic decrease, weight increases concomitantly. Obesity has been related to an increase in insulin resistance, type 2 diabetes, hypertension, and a higher risk of developing cardiovascular disease and other chronic disorders, many of which have been related to chronic inflammation as a consequence of the enhanced secretion of pro-inflammatory adipocytokines. Chronic inflammation, caused by obesity, and its related conditions (i.e diabetes, insulin resistance), may also play an important role in generating chronic stress, anxiety, depression and the development of several immune disorders, cancer and neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. The inhibitory effects of estrogens on neuro-inflammation have been highlighted recently and are a subject of intense research. Although estrogen deprivation seems to be the key element for the development of these chronic conditions, the contributing role of environmental and lifestyle factors, cannot be neglected.

(SYMP06) Insulin resistance/metabolic syndrome

Metformin and women health - what is new?

Andrzej Milewicz (PL)
Dept. of Endocrinology, Diabetology and Isotope Therapy Univeristy of Medicine Wrocław, Poland

It has been shown that metformin increases insulin sensitivity, inhibits liver gluconeogenesis by activating the adenosine 5′-monophosphate-activated protein kinase, reduces hyperglycemia and insulin level, prevents metabolic syndrome, has a positive impact on arterial blood pressure and lipids. Metformin may also reduce risk of cardiovascular events which are more frequent in women with visceral obesity, PCOS and postmenopausal women.. Metformin has recently been extensively studied and emerging evidence suggests metformin decreases hepatocyte triglyceride accumulation in NAFLD and prevents liver tumorigenesis. Interestingly, studies have also shown metformin reduces visceral fat, suppresses white-adipose-tissue (WAT) extracellular matrix remodeling, and inhibits obesity-induced inflammation. Metformin can also inhibit the generation and accumulation of advanced glycation end products (AGEs) and thereby prevents the development of the adverse structural and functional changes in myocardium as well as inflammation and insulinoresistance. Also several observational studies and meta-analysis showed that diabetic patients treated with metformin had a significantly lower risk of developing cancer or a lower cancer mortality.

(SYMP06) Insulin resistance/metabolic syndrome

The role of insulin resistance in benign breast disease

Svetlana Vujovic (RS)
Faculty of medicine, University of Belgrade, Clinic of endocrinology, diabetes and diseases of metabolism, Clinical center of Serbia

Main regulators of breast metabolism, estradiol, progesterone, prolactin, growth hormone, insulin like growth factor 1 – IGF1), activating intracellular signaling cascade (Erk, Akt, JNK i Ark/Stat), control cell function, proliferation and diferentiation of breast tissue. Insulin, cortisol and thyroxin have permissive role. Leptin induces epithelial cell prolifferation. Growth hormone directly increases expression of estrogen receptors (ER). Androgens suppress estrogen effects. Hiperinsulinism, as a proinflammatory factor, changes ratio between estradiol and progesteron (it is higher due to progesterone decrease) in the luteal phase inducing benign breast disease. While estradiol increases cell proliferation 230 %, progesteron inhibits it 400%. As well, progesteron inhibits renal tubulular reabsorption and increases cellular filtration rate, protecting from fluid retention, oedema and lowering capillar permeability. Progesteron induces RANKL. Breast carcinomas with RANKL expression have lower Ki67. Therapy of breast carcinoma with progesteron has the same effects as a Tamoxifen therapy. Risk for estrogen positive breast carcinoma is decreased, Meta analysis show correlation between MTHFR gen, C677T in axon 4 on C677T and breast carcinoma. Hypoestrogenism, high FSH and insulin resistance in the menopause, can induce breast carcinoma in women with inharited genetic mutations. Dynamic hormonal changes have to been detected in the luteal phase (not only day 21) due to confirm dagnosis. Benign breast diseas do not represent a „normal finding“ and has to be treated depending on etiological factors (progesterone, contraceptives, insulin sensitizers, anxyolitics, eating habits etc). This, completely different approach is more human, avoiding unnecessary breast surgery, psyhological disturbances and offering better quality of life.

(SYMP07) Progesterone, progestogens and their receptors

Translational research with progesterone in the uterus: from bedside to bench and from bench to bedside

Takeshi Maruo (JP)
Kobe Children's Hospital

This introduces a translational research initiated in 1993 by unexpected comment from a patient with symptomatic uterine myoma who used levonorgestrel-releasing IUS (Mirena) for contraceptive purpose. The patient informed us that she became very comfortable due to the remarkable reduction of heavy menstrual bleeding. Mirena insertion was found to inhibit cell proliferation and stimulate apoptosis in the endometrium, resulting in remarkable reduction in menstrual bleeding through the atrophic change of the endometrium. Despite the striking reduction in menorrhagia, MRI revealed that myoma volume during use of Mirena increased in some instances. These unexpected findings prompted us to characterize the effects of P4 on myoma cell growth *in vitro*. Treatment with P4 increased EGF expression while treatment with E2 enhanced EGF receptor expression. P4 treatment also augmented the proliferative activity in myoma cells, but not in normal myometrial cells. It became evident that P4 acts in combination with E2 as a promoter of myoma cell growth.
Consequently, the effects of selective progesterone receptor modulators (SPRMs; ulipristal and asoprisnil) on cell proliferation and apoptosis in cultured myoma cells were examined in comparison with those in cultured normal myometrial cells. Treatment with SPRM inhibited cell proliferation, stimulated apoptosis and reduced the expression of angiogenic factors such as VEGF and adrenomedullin and their receptors in myoma cells. Furthermore, SPRM treatment increased the expression of extracellular matrix metalloproteinase inducer and MMP contents, and decreased TIMP and collagen contents in myoma cells. SPRM treatment, however, did not affect those in normal myometrial cells. It is therefore likely that SPRM inhibits myoma cell growth in a cell-type specific manner in the uterus. These findings are meaningful for understanding the molecular mechanism underlying the effectiveness of SPRMs in a new non-surgical treatment of uterine myomas
Actually, the efficacy of long-term intermittent use of ulipristal has been demonstrated by randomized controlled studies conducted by Donnez J et al (Hum Reprod Updates 2016, Climateric 2019). Oral administration of ulipristal in patients with symptomatic myomas has been proved to reduce myoma volume and improve myoma-associated symptoms.

(SYMP08) SERMS and SPRMS

The challenge of SERMs

Santiago Palacios (ES)
Institute Palacios of Woman's Health

SERMs have an estrogenic agonist effect that may be beneficial either on the bone (Raloxifene, Bazedoxifene, Lasofoxifene) or on the vagina (Ospemifene) and which appears to be an effect dependent on the greater or lesser potency of the SERM (in postmenopausal women). The SERMs assessed appear to have antiestrogenic or neutral effects on the breast; Tamoxifen, Raloxifene, and Lasofoxifene have shown antiestrogenic effects in clinical trials; and Bazedoxifene and Ospemifene have shown antiestrogenic effects in preclinical trials but appear to be neutral in clinical trials to date. Most SERMs have been associated with a slightly increased risk of venous thromboembolism (VTE). The cardiovascular and cardiometabolic effects of SERMs in clinical trials appear to be positive or neutral. The adverse effects of Tamoxifen, relative to other SERMs, on the endometrium are well documented.
In the short term, it does not seem realistic to expect an ideal SERM to be estrogenic agonist in bone and vagina and antiestrogenis in breast and endometrium, and with added cardiovascular benefits. But each SERM that appears provides more information on efficacy and safety.
Another interesting concept would be TSEC, a combination of Bazedoxifene with conjugated Estrogens. Overall, literature data shows that TSEC significantly reduces vasomotor symptoms, improves sleep quality (increasing quality of life), and protects bone tissue and vaginal atrophy. There is no breast or endometrial stimulation with treatment, and cardiovascular risk is not increased, and may be an alternative to HT.
The rapid developments in molecular biology incorporates enormous possibilities on molecular biology, stem cells, cell biology in concurrence with genomics, functional genomics, genetics, proteomics, makes us optimistic, about the future of different estrogen modulators in not too long term in term.

(SYMP09) Endocrine disruptors

Endocrine disruptors and women health

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Endocrine disruptors (EDs) can act through classical nuclear or non-classical receptors. They can impact changes in metabolism of endogenous hormones, disrupt cross-talk between genomic and nongenomic pathways, and lead to changes in DNA methylation or histone modifications as well as genomic instability and as a consequence. Bisphenol A (BPA) is one of the most common plasticizers, present in a variety of objects of daily use, such as food packages, cans, electronic equipment, dental sealing, carbonless receipts, eye lenses, and water pipes. On account of its estrogenic properties, BPA is classified as an EDC or endocrine disruptor, which means it "alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations". The impact of BPA on variety of cells via classical signalling (estrogen receptors: ERα and ERβ) as well as via non-classical pathways was confirmed and widely described. BPA can be released as a monomer from these objects; hence, humans are constantly exposed to its endocrine disrupting properties from early life with the fetus exposed to BPA in the amniotic fluid and postnatal exposure coming in a variety of forms such as milk, plastic toys, plastic bottles, electronic equipment, food packages and cans, which leads to increase in BPA serum concentration. It is thought that this prolonged exposure to low doses of BPA may promote adverse health effects. The negative impact of BPA on human health was reported for reproductive disorders, infertility, miscarriages, prenatal development, and metabolic disorders including obesity, type 2 diabetes as well as coronary heart disease and hormone-dependent cancers. Moreover, recent studies have pointed its potential role in the PCOS pathogenesis.

(SYMP10) Contraception

Non-contraceptive uses of hormonal contraceptives

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Federación Mexicana de Colegios de Obstetricia y Ginecología

The main benefit of hormonal contraceptives is their effectiveness to regulate birthrate; being prevention of undesired pregnancy the main indication of hormonal contraceptives. Nonetheless with the use of hormonal contraceptives we can benefit some pathologies. My personal view then is to classify the use into 2 categories.
1.- Additional benefits of using hormonal contraceptives
2.- Non-contraceptive use

1. Additional benefits of using hormonal contraceptives:

It has been proven that the use of combined oral hormonal contraceptives reduces risk of endometrial and ovarian cancers.
It has been reviewed and the risk reduction of endometrial and ovarian cancer has been reported to be a 50% risk reduction, the one of benign breast disease is a 60% risk reduction and the risk reduction of pelvic inflammatory disease is reported to be 50% (Int J Endocrinal Metab 2013; 11: 41-47). Hormonal contraceptives are also useful to control menstrual migraine.

2. Non-contraceptive use:

Amongst the most frequent alternative non-contraceptive indications of hormonal contraceptives is the treatment of some alterations in gynecology.

a) These other disorders are hyperandrogenism, (acne, hirsutism, polycystic ovary syndrome). Particular oral contraceptives containing progestins like cyproterone acetate, dienogest, drospirenone and chlormadinone have shown to be effective medications to treat symptoms of hyperandrogenism (Contraception 2010; 82: 276-280).
b) Another alternative beneficial use is with dysfunctional uterine bleeding patients. It is worth to underscore that estrogen-progestin association prescribed orally is a very good cycle regulator and in the case of patients with heavy menstrual bleeding, the use of levonorgestrel intrauterine system.
c) These are also administered to patients with infertility in order to program cycles for assisted reproduction.
d) Finally, alternative use hormonal contraceptives are administered to control dysmenorrhea and dysphoric disorder which is its most severe expression as noted above.

In conclusion, hormonal contraceptives bring many beneficial effects. Their alternative use in the daily practice of gynecology shows their effectiveness which in turn brings changes to the quality of life of women. Its cost-benefit ratio is good as well as long as risk-benefit ratio is always assessed.

(SYMP10) Contraception

Contraception: MEC of WHO – what should be changed?

Alfred Mueck (DE)
University Women's Hospital of Tuebingen

The MEC of the WHO for contraceptives are an excellent guide to find a choice of the contraception especially for problem-patients e.g. with risk of venous thromboembolism (VTE). However, these guidelines mostly are based on the clinical evidence rather on biological plausibility or pharmacological knowledge derived from mechanisms. Since the impossibility to perform placebo-controlled clinical endpoint studies in the field of contraception and the limitations to conclude from observational studies on topics investigating only rare events we are suggesting a change in this policy i.e. the science of pharmacology, biology and biochemistry should be considered to be equivalent to the discipline "medicine" especially if good clinical studies are missing. This is true not only for the MEC, but also for general assessments of WHO in context with hormones, e.g. the WHO-statement, that estrogens are "carcinogenic" for women, in our view is wrong! Biochemical and molecular-oncological research have shown that additional factors delivering unrestricted abundant oxidative cell stress is necessary that this WHO-statement could be correct. To give practical examples with respect of MEC - the importance of different pharmacology of progestogens regarding their pharmacodynamic and pharmacokinetic actions should be added into the decision finding for the choice of the contraceptive, e.g. the very strong vasoconstrictory effect of high dosages of MPA (i.e. DMPA). Another example are the different situations of VTE risk, with in our view wrong MEC for DMPA and NET-EN: Their MEC is assessed as "2", the same like for POP (i.e. desogestrel pill). However, experimental research point on increased VTE-risk using DMPA because of its glucokorticoid side effects, which does increase thrombin-2 activity (and also four observational studies suggest higher VTE-risk). Especially wrong in the MEC guidelines is the assessment of NET-EN considering that NET can be metabolized to a small degree to EE, and due to the high NET dosages using NET-EN the EE-concentrations are the same as using COC containing 30μg EE. So the MEC should not be like for POP but should be exactly like for COC (i.e. MEC 4 instead of 2). We also suggest to adapt the MEC to possible different genetical situations, e.g. the very low basic VTE-risk for Asian women should be considered, which we have investigated within an large observational study in our Beijing hospital (5 million Chinese women).

(SYMP11) Dealing with side effects of hormone contraception

Influence of combined oral contraceptives and the menstrual cycle on sexual function in young women

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Karolinska Institutet

Sexuality in women is complex and influenced by several factors. In young women, the use of oral contraceptives (OC), as well as hormonal fluctuation during the menstrual cycle have been reported to affect sexuality and mood. However, the studies have shown inconclusive and sometimes contradictory results. In a large randomized, placebo-controlled trial, we have previously demonstrated negative impact of a levonorgestrel-containing OC on overall sexual function and a significant reduction in general well-being but no effect on depressive symptoms in 340 young healthy women. The present study was a secondary analysis of the same trial with the aim to investigate if there were differences in sexual function, general well-being and mood between different phases of the menstrual cycle in the placebo group (n=168). At baseline, all women were investigated in the follicular phase. At 12 weeks follow-up, the classification in different phases of the menstrual cycle in the placebo group was based on serum levels of FSH, LH, estradiol and progesterone. The change in sexual function (the Profile of Female Sexual Function), well-being (Psychological General Well-Being Index (PGWBI)) and mood (the Beck Depression Inventory (BDI)) from baseline (follicular phase) to the other phases (ovulation and luteal phase) was analyzed. Among the participants, 93 (55%) were in the follicular phase, 36 (21%) were in the ovulatory phase, 29 (17%) were in the luteal phase, and 10 (6%) could not be classified. We found no significant change in sexual function between different phases of the menstrual cycle. However, being in a relationship had a significant positive influence on overall sexual function. Furthermore, there was no significant change in general well-being between the cycle phases. The only signficant change was a decrease in depressed mood (BDI) in the luteal phase compared to the follicular phase ($p<0.05$). In conclusion, young healthy women seem to have small or no variations in their sexual function and general well-being during the menstrual cycle, whereas the luteal phase could have a negative impact on depressed mood. These results contribute to the knowledge of normal variation in sexuality, well-being and mood during the menstrual cycle in healthy young women.

(SYMP11) Dealing with side effects of hormone contraception

Contraception in women with BRCA1/BRCA2 mutation

Gabriele Merki (CH)
University Hospital

Breast cancer (BC) is the most frequent cancer diganosis in women (lifetime risk 10%). In women without a special predisposition use of combined hormonal contraception (CHC) is associated with a relative risk of 1.19. This risk is based on 68 cases in 100000 person-years of use and corresponds to 13 additional BC cases in 100000 person-years.
The BRCA 1 and BRCA 2 mutations occur with a frequency of 2.9% in the population. They are associated with a much higher risk of breast cancer (BRCA 1: 54-75%; BRCA 2: 45%). To identify women at risk the family history with a relative on mother`s or father`s side, who had breast cancer diagnosed before age 50 is helpful. The probability to develop breast cancer is higher in BRCA 1 mutation carriers if they use CHC (RR around 1.3). This adds to the already very high baseline risk of 54-75%. BRCA 2 carriers have an around 50% risk to develop breast cancer. CHC use beyond 5 years causes a twofold increase in risk, according to two studies, however onte trial did not find an increase in BC risk. Altogether for both mutations benefits of CHC use have to be carefully be weighted against the increase in breast cancer risk. Duration of use should be limited and use of copper devices should be taken into consideration. It is not known inhowfar POCs and LNG-IUSs have an impact on the individual risk. Both are associated with an increase in breast cancer in women without hereditary predisposition.

(SYMP12) Premenstrual disorders: what we know and what we do not know about the late-luteal enigmatic condition

To what extent and how is autonomic nervous system activity associated with the diverse psychophysiological symptoms in the premenstrual phase?

Tamaki Matsumoto (JP), Miho Egawa (JP), Tetsuya Kimura (JP), Tatsuya Hayashi (JP)
[Matsumoto] Shitennoji University, [Egawa] [Hayashi] Kyoto University, [Kimura] Kobe University

Regardless of nationality, up to 90% of reproductive-age women report experiencing one or more symptoms premenstrually that can alter behavior and well-being and affect family, friends, and working relationships. Although no clear consensus exists as to the underlying causes of this enigmatic condition, commonly known as premenstrual syndrome (PMS) or more severe PMS, premenstrual dysphoric disorder (PMDD), increasingly consistent research findings point to clinically relevant biopsychosocial factors that contribute to symptomatic expressions, which, if addressed, can lead to effective treatment options. The autonomic nervous system—a critical player in the integrity of mind-body connection as the functional driver of general health and wellness—plays vital roles in dynamically controlling the response of the body to a range of external and internal stimuli and ingeniously modulating biological homeostasis. Instability, or even a slight disorder of the system, therefore, could induce broadly ranged psychophysiological phenomena and, ultimately, far-reaching adverse effects on health. As a matter of course, the question emerges: to what extent and how does the autonomic nervous system contribute to premenstrual disorders? A series of studies on women's health in the authors' laboratory has non-invasively measured the behavior of autonomic nervous system activity, by using reliable biomarkers, such as heart rate variability and salivary chromogranin A, among women who report varying degrees of PMS/PMDD during the menstrual cycle. The authors have also investigated the efficacy of therapeutic modalities, including aromatherapy, to alleviate the symptom complex from the perspective of autonomic function. Based on the findings of the previous research, together with classic and contemporary literature, this presentation will discuss the extent to and the manner in which autonomic nervous system activity relates to the menstrual cyclicity of psychophysiological conditions. It will also cover the following topics as possible agents affecting susceptibility to PMS: lifestyle factors, subjective perception of health, vulnerability to stress, personality traits, socio-environmental stimuli, and cultural backgrounds. Through exploring the potential interrelationship between autonomic nervous system activity and the complex web of bio-psycho-social factors relating to PMS, the presentation will probe altered autonomic function as a viable cause or effect of PMS.

(SYMP13) Endometriosis - updates from basic science

Neurotrophins and cytokines in endometriosis pain

Robert Taylor (US)
University of Utah

Context

The association of pelvic pain with endometriosis was recognized since Sampson's earliest publications in the 1920s. Yet, the mechanisms by which ectopic endometrial implants cause pelvic pain remain unknown. Correlations between visible disease burden and extent of pain are poor, leading investigators to postulate that invisible, biochemical mediators translate pain stimuli from the lesions themselves. Indeed, nociceptive nerve fibers innervating endometriosis implants and the eutopic endometrium of women with endometriosis have been identified. We hypothesized that coordinated nerve and capillary recruitment to nascent lesions ("neuroangiogenesis") was involved.

Objective

To identify targetable growth factors, cytokines and signaling pathways that stimulate local neurotrophin production within endometrial and endometriosis tissues.

Methods and Patients

Antibody microarrays and immunohistochemistry (IHC) of biopsies were performed in a case-control (n=21, n=16) study. *In vitro* experiments with isolated primary human endometrial stromal cells (ESC) derived from eight volunteers with endometriosis were used to test the hypothesis that IL-1β regulates neuroangiogenic factors. Growth factor synthesis and signal transduction pathway(s) were examined. IL-6 (by ELISA) was used as a positive control for IL-1β action. Validated, specific kinase inhibitors were used to identify canonical signaling pathways of IL-1β. Statistical differences were accepted when two-tailed Student's t tests or analysis of variance (ANOVA) with Scheffé post hoc tests yielded $P<0.05$.

Results

BDNF was found to be the dominant neurotrophin in endometrial tissue and was differentially overexpressed in cases of endometriosis. Its IHC localization was concentrated in the lesions, and was proximally accompanied by blood vessels and macrophages. *In vitro*, the EC (effective concentration)50 of IL-1β in ESC was ~2 ng/ml for BDNF mRNA and protein synthesis. BDNF was time- and dose-dependently stimulated 3±2-fold by IL-1β ($P<0.05$), an effect that was blocked by the natural antagonist, IL-1ra. Inhibitors of the NF-ϰB and c-Jun N-terminal kinase (JNK) pathways also significantly reduced the activation of BDNF by IL-1β.

Conclusions

The findings support the hypothesis that IL-1β in the endometriotic microenvironment can activate the expression of BDNF mRNA and protein, which encode a neurotrophin with the potential to mediate neuroangiogenesis and pain in endometriosis lesions.

(SYMP14) Ultrasound evaluation of pelvic endometriosis

Can we diagnose endometriosis with ultrasound rather than laparoscopy?

Steven Goldstein (US)
New York University School of Medicine

Various societies have guideline statements on the role of imaging in diagnosing endometriosis. ACOG states that transvaginal ultrasound (TVUS) is the, "preferred imaging technique when assessing endometriosis and/or deep endometriosis of the rectum or rectovaginal septum." The American Society of Reproductive Medicine (ASRM) differs. It has stated, for both TVUS and MRI, "that imaging modalities have not been found to increase diagnostic accuracy." Perhaps the Canadian Society (SOGC) stance, in my opinion, is the most reasonable. It states TVUS is, "the first line investigational tool for suspected endometriosis," whereas MRI, "could be required if deep endometriosis is suspected."

Hudelist et al. reported a sensitivity for endometriosis of approximately 30% with pelvic examination alone, but 96% with pelvic examination plus TVUS. However, this is utilizing TVUS as an anatomic image, which previously had been the mainstay of how it was being performed. Now we need to employ "dynamic imaging." Careful examination of the work by Okaro et al. underscores this point. They evaluated 120 women who had chronic pelvic pain. What they called "hard markers" (ovarian endometriomas, hydrosalpinges) had a 100% correlation with laparoscopic findings (24 of 24 cases). "Soft markers" defined as reduced ovarian mobility, site-specific pelvic tenderness, or the presence of loculated peritoneal fluid were predictive of pelvic pathology in 37/51 (73%) of women. Many of these women, if examined by a typical anatomic ultrasound survey, would have been classified as "normal." This underscores the increasing importance of the use of dynamic scanning in patients with chronic pelvic pain. These data further suggest an empiric course of treatment may be appropriate as 61 of 75 (81%) of the women evaluated by transvaginal ultrasound had such a need for treatment confirmed laparoscopically.

All who perform or order transvaginal ultrasound should do or expect to be done, a dynamic assessment in real time looking for tenderness, decreased mobility and non-anatomically located ovaries. When adhesions exist, ovaries may appear anatomically normal in size and appearance but not necessarily in location. While not diagnostic of adhesions, when coupled with pain on movement with a vaginal probe, or a lack of mobility of such ovaries, one's index suspicion for pathology like endometriosis should be greatly increased.

(SYMP15) Endometriosis' therapies

Medical management of endometriosis, present and future with special reference to MHT in the patient previously diagnosed with endometriosis

Tobias De Villiers (ZA)
Stellenbosch University

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, that induces a chronic, inflammatory reaction. It is a chronic and incurable disease that causes pain and is associated with infertility. Although surgery will continue to be an important mode of treatment, hormonal treatment is now favored as first-line therapy. Endometriosis is considered an estrogen dependent disorder. Endometriotic tissue has higher local availability of estradiol that may be explained by higher aromatase enzyme expression and impaired conversion of potent E2 to less potent E1. In normal endometrium progesterone facilitates the transition of proliferative endometrium to secretory endometrium. In endometriotic tissue this effect is blocked by increased local endogenous E2 resulting in incomplete endometrial transition. This disables a critical protective mechanism against estrogen induced growth of endometrial tissue. Hormonal therapy of endometriosis entails the inhibition of estrogen activity and/or the amplification of progesterone effects. The success of the modern progestin dienogest in the treatment endometriosis, is evident in multiple recent publications. Side-effects are modest and bone-loss restricted to the young. Dydrogesterone has been known for many years to have a similar effect with the advantage of being safe in early pregnancy, although it entails a more complicated regime compared to a single 2mg daily tablet of dienogest. Progestins have largely replaced the combined oral contraceptive pill and danazol in endometriosis treatment. GnRH-analogs/antagonists are effective but causes hypoestrogenic symptoms and bone-loss necessitating ad-back hormone therapy. Future therapies include selective progesterone or estrogen receptor modulators and aromatase inhibitors. Although the postmenopause generally favors eradication of endometriosis because of lack of ovarian estrogen production, this is not always the case. Endometriosis can persist in a low systemic estrogenic environment by local estrogen production in ectopic endometrial tissue by autocrine and paracrine mechanisms. In menopause, endometriosis can persist, be reactivated or undergo malignant transformation. If MHT is indicated, it should be opposed MHT to reduce the risk of malignant transformation. A progesterone with the smallest potential risk to the breast should be considered. Surgery with biopsy should be considered in menopausal endometriosis.

(SYMP16) Microbioma

Uterine microbiota in implantation and human pregnancy

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Igenomix Foundation

The microbiota in the urogenital tract of healthy reproductive age women is mainly composed of bacteria from the Lactobacillus genus; however, structural or compositional variations of this microbiota, may impact the function of reproductive organs leading to infertility or other pathological conditions. Lately, the assessment of the endometrial microbiome has been proposed as a new factor to be considered in infertile patients to improve our understanding of the reproductive function and develop personalized medicine in assisted reproductive technologies.

(SYMP16) Microbioma

Novel discoveries on vaginal microbiome: is there a future role for Lactobacilli therapeutic application?

Gary Ventolini (US)
Texas Tech University Health Sciences Center

Worldwide, a major challenge we currently phase as humans is antibiotic resistance, almost 700,000 patients die yearly worldwide due to drug-resistant bacterial infections. Bacteria very rapidly grow and reproduce and have developed protective mechanisms to survive, some of them becoming so called superbugs.
Strategies to solve this problem have been proposed. Including are: identify antibiotic resistance genes, fingerprint microbiomes, find bacterial weaknesses to be target by novel antibiotics, prodrugs, hybrids, peptides, nanomaterials, plants, marine products, CRISP-Cas9 genomic manipulation, novel cultures and delivery systems, vaccines. Others already proposed like antibiotic stewardship are problematic to implement worldwide and new antibiotics research are challenging to accomplish.
Least explored methods although beneficial and low risk are by natural bacterial products: anti-biofilms and anti-microbial peptides. Such as Lactobacilli products from the normal vaginal microbiome. Because their therapeutic utilization carries excellent tolerance and low rejection probability from the immune system.
In 2017, our research group at Texas Tech University HSC reported: “Lactobacillus strains inhibited the growth and biofilm development by Pseudomonas aeruginosa”.
In October 2019, we published the effectiveness of Lactobacilli gasseri (Lg) supernatant against Pseudomonas aeruginosa (Pa). In thermal injury murine model, a Lg single injection following injury and Pa infection, reduced mortality to 0 % preventing sepsis. A Lg second injection 24 h after, eliminated Pa from the wound. In dorsal excision infection model, either Lg or ceftazidime (C) wound treatment significantly reduced mortality rate among infected mice, while combining Lg with C eliminated mortality.
These results suggest the potential of Lg in preventing sepsis from Pa in severely burned and other immunocompromised patients.

(SYMP17) Implantation

Does inflammation perturb the embryo-endometrial dialog?

Robert Taylor (US)
University of Utah

Context

In women and mice, implantation is controlled within a vulnerable window of uterine receptivity. Infectious conditions (e.g., chronic endometritis), or sterile inflammation (e.g., endometriosis, PCOS, and miscarriage) reduce fecundity. Studies from our laboratory indicate that the gap junction protein connexin (Cx)43 is a key implantation factor. In genetically engineered, loss-of-function mice, targeted Cx43 knock-out reduced litter sizes and antagonism of Cx43 by pharmacological agents or siRNA in decidualized human endometrial stromal cell (ESC) cultures corroborated these findings. We hypothesized that inflammation might reduce fecundity by interference with ESC decidualization.

Objective

To identify potential fertility-compromising pathways that might be corrected by anti-inflammatory therapeutics.

Methods and Patients

Human ESC derived from parous women with regular menstrual cycles were cultured and decidualized *in vitro* with hormones (10 nM 17β-estradiol, 100 nM progesterone, and 0.5 mM dibutyryl cyclic adenosine monophosphate) for 3-7 days. Some cultures were exposed to IL-1β to mimic inflammation. ESC shape, secreted biomarkers (prolactin, IGFBP-1, IL-11 and VEGF) and other differentiation indicators (Cx43, ERα, PR-A and –B) were quantified The data were normally distributed and differences were accepted when two-tailed Student's t tests yielded $P < 0.05$.

Results

IL-1β treatment dose-responsively inhibited Cx43, prolactin and VEGF with an IC50 ~0.2 nM. The phospho-p65 subunit of NF-ϰB was rapidly (<20 min) translocated into the nucleus, corresponding to a rapid downregulation of IϰBa. Over the next 48 h a dramatic decrease in VEGF also was noted. Evidence of decidual morphological changes induced by estrogen, progesterone and cAMP was demonstrably blunted by IL-1β and the cleaved caspase 3 indicated activation of ESC apoptosis. Finally, ER-α and PR-A and -B concentrations were all reduced in cells treated with IL-1β.

Conclusions

Cx43 as well as traditional biomarkers of ESC differentiation were suppressed after exposure to IL-1β. These detrimental effects could be reversed by inhibition of IL-1β or its downstream signaling molecules, NF-ϰB and ERK1/2. Increased cell "rounding" and upregulation of decidualization markers also were noted when siRNA was used to block ERK1/2. We propose that drugs that oppose effects of IL-1β might enhance decidualization in women with inflammation-associated uterine factor infertility.

(SYMP19) Recent development in IVF

Which patients need LH in addition to FSH

Bruno Lunenfeld (IL)
Bar Ilan University

The role played by LH in the normal ovulatory cycle is known since the discovery of the two cell theory however only recently do we know that LH has different roles in different parts of the cycle, In the early phase LH acts on the thecal cells to produce androgens necessary for the recruitment phase, and sensitizing the granulosa cells FSH receptor. In the mid cycle LH stimulates thecal cell to produce testosterone as a substrate for the production of estrogens and finally it is responsible for the maturation of the oocyte and induction of ovulation. Following ovulation. LH is responsible to maintain the corpus luteum until in pregnancy the placenta will take over. Although only less of 1% LH receptor need to be occupied LH deficiency is a major cause of failure of endocrine dynamics leading to pregnancy. LH deficiency can manifest in females as delayed puberty, or at any age, resulting in productive abnormalities that can be dramatic or subtle. LH deficiency can result from a myriad of anterior pituitary dysfunctions. Hypothalamic suppression of LH can occur in women under physical or metabolic stress. Genetically it can be induced by nucleotide polymorphisms of LHCGR receptor (LHCGR 291Asn/Ser, LHCGR 312 Ser/Asn (rs2293275) or LH polmorphisms (V-betaLH genotype,). Iiatrogenic it can be induced by the use of GnRH long agonist protocol. Partial LH deficiency has been reported in antagonist cycles in which intra-cycle LH levels were very low. In such cases women given LH supplementation had significantly higher number of eggs and higher live birth rates were reported. The ageing ovary has less functional LH receptors. Aging women also may have less potent and biological active LH bioactivity. LH in the aged ovary Up-regulates growth factors, reduces apoptosis and enhances the expression of anti-apoptotic proteins. Resting levels of LH (1-10 UI/L) should be sufficient to provide maximal stimulation to theca cells”During ART treatment. LH deficiency may cause poor ovarian response, corpus luteum deficiency, and problems with implantation. Increased frequency of low LH episodes will increase probability of pregnancy loss. Addition of LH from day 1 of stimulation is necessary in patients with Hypogonadotropic – hypogonadism and will yield better number of oocytes retrieved a well as implantation rates in severe poor responders, in hypo-responders and in women older than 35 years.

(SYMP19) Recent development in IVF

The use of nolasiban, a novel oxytocin receptor antagonist, prior to embryo transfer: does it help?

Ernest Loumaye (CH)
ObsEva SA

The oxytocin receptor antagonist nolasiban was investigated in three clinical trials for its potential to improve pregnancy and live birth rates in women undergoing fresh embryo transfer (ET) following *in vitro* fertilization (IVF).
The trials were randomized, double-blind, placebo-controlled studies. Nolasiban (or placebo) was administered as a single oral dose 4 hours before ET to women aged < 38 years with ≤ one previous failed cycle. All participants had undergone a GnRH antagonist protocol, a single hCG dose to trigger ovulation, IVF or ICSI with their own eggs, had ≥ one good quality embryo, and received standardized luteal support with vaginal micronized progesterone.
Efficacy endpoints included ongoing pregnancy rate (OPR) at 10 weeks post-ET, and live birth rate. Maternal, fetal, neonatal and infant safety outcomes were assessed.
IMPLANT1 was a dose ranging trial of 100, 300, and 900 mg nolasiban in 247 women undergoing Day 3 single ET (SET) or double ET. Overall, the 10-week OPRs were 29.2% in placebo and 41.2% in the nolasiban groups and were highest in women receiving 900 mg (45.0%).
IMPLANT2 tested 900 mg nolasiban versus placebo in women undergoing Day 3 (n=388) or Day 5 (n=390) SET. A significant absolute increase of 7.1% (95%CI 0.04, 14.1, p=0.031) was observed for OPR in the overall Day 3/Day 5 nolasiban group. Analyzed separately, the OPR increase was statistically significant in the Day 5, 11.2% (95%CI 1.1, 20.8, p=0.034), but not in the Day 3 subgroup, 3.1% (95%CI -7.1, 13.2, p=0.477).
IMPLANT4 tested 900 mg nolasiban versus placebo in 807 women undergoing Day 5 SET. There was no significant increase in OPR, 1.4 (95%CI -5.33, 8.12, p=0.745).
Overall, safety outcomes of nolasiban and placebo were similar.
In a meta-analysis of all three trials, the OPR in subjects receiving 900 mg nolasiban was 38.5% versus 33.6% with placebo (OR 1.25; 95%CI 1.02, 1.52, p=0.029).
In conclusion, the potential of nolasiban to increase pregnancy and LBR observed in IMPLANT 1 was confirmed in IMPLANT2 but not in IMPLANT4. The meta-analysis suggests nolasiban may increase OPR. Further analyses will assess whether certain baseline factors may influence responses to nolasiban.

(SYMP22) Perimenopause

Inflammation and the metabolic syndrome during the menopausal transition

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During the female menopausal transition there is a gradual decrease in the secretion of ovarian estrogens. This has been related to bio, psycho- and social changes. Estrogens play an important role in maintaining many female systems in appropriate functioning, and as a direct or indirect consequence of this progressive estrogenic decrease, and as women age, weight increases proportionally. Increasing weight enhances the risk of suffering the metabolic syndrome (METS). This syndrome is group of lipid and non-lipid factors that increase cardiovascular risk. Diagnosis is met when three or more factors are positive (i.e. abdominal obesity, high triglycerides, low HDL-C, high fasting glucose and/or high blood pressure levels). The most relevant feature of the syndrome is abdominal obesity. The METS is considered a pro-inflammatory state with high secretion of adipocytokines which subsequently produce endothelial dysfunction and increases cardiovascular morbidity and mortality and the risk of developing diabetes. Although the prevalence of the METS increases significantly after the female menopause, currently due to worldwide changes in diet and lifestyle habits, and the fact that women increase body weight during the menopausal transition long before menopause onset, the trend will be that an increasing number of women before the menopause will have the METS. This is important because our research indicates that pro-inflammation is already present during the perimenopausal stage; thus, after the menopause women will be at higher cardiovascular risk. This presentation will aim at presenting an overview of the syndrome before and after the menopause, focusing on inflammation and endothelial dysfunction.

(SYMP22) Perimenopause

The endocrinology of menopause transition

Amala Nazareth (AE)
Prime Healthcare Group Dubai UAE

The female reproductive axis is unique in that it reaches a senescent state when other organs in the body are generally healthy. The process of oocyte depletion, which begins before birth and ends with menopause, cannot be predicted precisely by chronological age, as its age of onset varies greatly between women. However, a clinical staging system exists, which makes it possible to identify where a woman is in her process of reproductive aging based on her bleeding patterns, which is a better predictor than her age. Staging is useful for several reasons, among them providing a means to attribute women's symptoms during this time to menopausal changes, predicting time to final menstrual period, and identifying health risks. There are now well described symptoms that are linked to specific time points along the menopausal transition, thus validating the concept that menstrual cycle disruption, along with its underlying hormonal changes, are responsible for the common symptoms of the menopausal transition. Moreover, evidence is accruing that at least some menopausal symptoms not previously attributed to estrogen deficiency are successfully treated by exogenous hormones.

(SYMP22) Perimenopause

Mood disorders during reproductive transitions: circuit and cellular substrates of risk

Peter Schmidt (US), Shau-Ming Wei (US), Howard Li (US), Neelima Dubey (US), Jessica Hoffman (US), David Rubinow (US), Karen Berman (US), David Goldman (US)

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Premenstrual Dysphoric disorder (PMDD) represents the convergent effects of the ovarian steroid trigger and a susceptibility to experience affective dysregulation, since the same biological trigger is without effect on mood in women lacking the susceptibility. We have investigated the possible substrates of this differential steroid behavioral sensitivity in studies using both brain imaging and cell culture methods, respectively.

Women with PMDD (n=20) and controls (n=43) underwent resting state H215O-PET during three hormone conditions: induced-hypogonadism, estradiol (E2) and progesterone (Prog) to explore interactions between diagnosis and hormone conditions in the brain. Concurrently, lymphoblastoid cells (LCLs) from women with PMDD (n=10) and controls (n=9), and neuroprogenitor cells (NPCs) (n=4/group) were derived and exposed to E2 or Prog. RNA-seq and network analyses identified differentially expressed genes (DEGs) and gene networks, including ESC/E(Z). qRT-PCR was performed in a replication sample of LCLs (n=24/group)

There was a significant diagnosis-by-hormone interaction in the subgenual cingulate ($F_{2,57}=7.4$, $P_{FDR}<.05$): compared with controls, women with PMDD had significantly decreased resting rCBF during E2 and Prog ($P<.03$ both comparisons) but not during hypogonadism. LCLs showed increased baseline mRNA expression in PMDD over controls within the 13 ESC/E(Z) gene-family including increased expression in MTF2, PHF19, and SIRT1 ($P<0.05$), and these findings were confirmed with qRT-PCR and by RNA-seq in both a separate sample of LCLs and in NPCs, respectively. DEGs were observed after Prog in controls but not PMDD (EED, EZH2, MTF2, $P<0.05$) and after E2 in PMDD but not controls (JARID2, $P<0.05$). Additionally, in women with PMDD, ESC/E(Z) gene expression significantly correlated with the change in resting rCBF between Prog and Lupron alone (Pearson $r=-0.807$, $P=0.016$). Finally, preliminary network analysis of E2-exposed LCLs implicates DEGs involved in intracellular calcium regulation (NUCB1, GCC2, TRPM7; $P<.01$) in PMDD.

These data demonstrate that the differential behavioral sensitivity in women with PMDD is paralleled by rCBF (*in vivo*) and cellular transcription (*in vitro*) responses to ovarian steroids.

(SYMP23) Menopause: from symptoms to risks

Hot flashes and cognition: the role of cortisol

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Cortisol levels increase immediately after an objectively measured hot flash, and increase during the late menopausal transition, a menopausal stage characterized by both vasomotor symptoms (VMS) and cognitive complaints. The cortisol awakening response (CAR), a physiological response characterized by a rise in cortisol after awakening from sleep, is frequently used as a marker of hypothalamic-pituitary-adrenal (HPA) activity. Understanding the relationship between VMS-related changes in CAR and daily cortisol can provide novel insights into HPA function as a mechanism contributing to alterations in cognitive function in midlife women. To understand these relationships we measure VMS objectively using ambulatory skin conductance monitors, CAR, and cognitive performance with standardized neuropsychological test batteries. Findings reveal that objective VMS are associated with increased cortisol levels upon waking, and that higher cortisol levels are associated with alterations in cognitive functions involving the hippocampus and prefrontal cortex. Overall, these and other data indicate that VMS-related alterations in the HPA axis might contribute to cognitive difficulties at midlife.

(SYMP23) Menopause: from symptoms to risks

Oral versus transdermal estradiol - difference beyond cardiovascular risks

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With respect of efficacy there are mostly no relevant differences between oral and transdermal estradiol (E2) application (if equivalent dosages are considered), i.e. with both application forms the same benefit can be achieved to reduce climacteric complaints and/or to prevent osteoporosis. However, there are some exceptions like stronger efficacy in smokers with transdermal estradiol due to the strong and fast hepatic metabolism using oral estradiol treatment. In addition often a better effect for treatment of migraine or/and headache complaints with transdermal E2 can be achieved due to more constant E2-levels which can avoid strong changes in vascular tone, keeping constant blood flow and constant vasodilatation. Constant E2-levels also are the reason for the better effect of transdermal E2 for treatment of AUB-0 bleeding problems stabilizing the endometrium, i.e. avoiding up and down proliferation – the reason for AUB. Relevant differences exist in the risk profile. Besides the well-known higher cardiovascular risks of oral compared to transdermal E2 (i.e. higher risk of venous thromboembolism, ischemic stroke and certain types of coronary heart diseases) oral E2 in contrast to transdermal E2 increases the triglycerides, but does have the benefit to reduce HDL in contrast to transdermal E2. Oral E2 especially is indicated for symptoms of hyperandrogenemia or its clinical consequences (acne, seborrhea, PCOS, certain types of metabolic syndrome, central obesity). In hypertensive patients transdermal should be preferred, because in contrast to oral estrogens up-regulation of the RAAS (via stimulation of angiotensinogen) is avoided. Also for the treatment of diabetes-patients mostly transdermal E2 is the better choice, because diabetes often is combined with hypertriglyceridemia. Moreover, transdermal E2 confers lower risk of gallbladder diseases because of lower risk of cholelithiasis and also should be preferred in patients with risk of pancreatitis. From own and other research we suggest, that transdermal E2 may also avoid the development of certain types of breast cancer, since the precursors of potential carcinogenic E2-metabolites (quinones) are not produced - a mechanism, which, however, needs additional excessive oxidative cell stress for example during smoking or from toxic environment. Thus, in summary, mostly transdermal application is the better choice with respect of reducing cardiovascular and non-cardiovascular risks.

(SYMP24) Estradiol, steroid-regulated genes, brain function and behavior: of mice and women

Cross-species epigenetic signature induced by ovarian hormones

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Sex hormones and their neurosteroid metabolites contribute to the establishment of sex differences as well as the regulation of the mental state. In many women, natural fluctuations in circulating ovarian steroids across the menstrual cycle are associated with negative emotions. We investigated an animal model of genetic sensitivity to the ovarian hormone, estradiol to identify genes conserved within females across species that may also serve a greater biological purpose, such as adaptation to environmental challenges. We hypothesized that a human genetic variant of the brain neurotrophic factor gene, BDNF Val66Met, that is a modifier of psychiatric disorder susceptibility, is also a risk factor for mental disease associated with ovarian hormone fluctuation.
Using whole-genome RNA-sequencing, incorporating mouse and human studies, we found that exogenous 17β-estradiol (E2) affects the epigenome in a BDNF Val66Met knock-in mouse model, in a way that recapitulates the genomic and behavioral hallmarks of premenstrual dysphoric disorder (PMDD). Mice heterozygous for the BDNF Met allele (h-Met) were administered E2 in drinking water for six weeks, before dissection of the ventral hippocampus, while lymphoblastoid cell lines (LCLs) were obtained from women with PMDD, and subsequently treated with E2. Wild-type mice and control women with or without treatment where also included in the study.
Through integrating RNA sequencing datasets, we identified a number of common orthologues that were induced by E2 in both species and both tissues. A GO analysis of commonly regulated genes revealed, among the top 10 enriched pathways, two major epigenetic clusters, namely transcription and covalent chromatin modification. Common epigenetic genes were entered into GeneMANIA, to identify genes that are correlated to the interaction network. The epigenetic interactome that overlapped women and mouse included, among others, the ESC/E(Z) complex genes SUZ12, EZH2, HDAC2, and JARID2. ESC/E(Z) complex, an effector of response to ovarian steroids, has been recently associated with PMDD. Thus, E2 add-back induced intrinsic, common epigenetic modifiers in the ventral hippocampus of ovariectomized h-Met mice and LCLs of PMDD women that transcended species and cell types. Animal models of ovarian hormone sensitivity shed light on epigenetic markers conserved across species relevant for novel diagnostic and therapeutic interventions.

(SYMP24) Estradiol, steroid-regulated genes, brain function and behavior: of mice and women

Differential effects of estradiol exposure in women

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The risk of depression increases 2-3 fold for women during the menopause transition compared to premenopausal women. Additionally, peri/postmenopausal women with even minor depression are at an increased risk of cardiovascular mortality (Wassertheil-Smoller et al, 2004). Clinical studies show both the therapeutic benefits of estradiol (E2) in perimenopausal depression (PMD) and the symptom-provoking effects of E2-withdrawal (E2WD) in women with past PMD but not those without past PMD. Thus, it has been suggested that a heightened sensitivity to changes in E2 may contribute to the onset of PMD.
We hypothesized that the differential affective/behavioral responsivity to E2WD in PMD could be observed on a cellular level. To test this hypothesis, we used lymphoblastoid cell lines (LCLs) derived from women with a past PMD (n=8), or asymptomatic controls (AC) (n=9). These LCLs were examined in 3 different experimental conditions: 1) vehicle-treated media, 2) E2-treated media, or 3) E2-treated media which was changed to vehicle-treated media and collected 24 hours after (to mimic E2WD) on a cellular level. Cells were collected and examined for changes in gene expression levels using whole-transcriptome RNA sequencing. EDGE-R analysis of differential gene expression revealed significant RNA expression changes between women with PMD and AC in all 3 treatment conditions, as well as several molecular pathways that appear to be differentially altered in women with PMD. The gene CXCL10, which has been previously linked to cardiovascular disease, was significantly upregulated in LCLs from women with PMD, and had the most extreme increase in transcription in the E2WD treatment condition. In contrast, a gene coding an enzyme CYP7B1, responsible for the metabolism of DHEA and pregnenolone, also was significantly upregulated in women with PMD, but E2 treatment conditions had no further effect on transcript expression. qRT-PCR using a larger cohort of LCLs with a somewhat broader PMD phenotype confirmed CXCL10 was significantly increased in PMD after E2-withdrawal ($t(37)=2.8$, $p<0.009$).
Our results suggest that the differential behavioral responsivity to changes in E2 exposure in PMD is linked to intrinsic differences in cellular gene expression. Clinically, genes such as CXCL10 and CYP7B1, and their corresponding dysregulated proinflammatory and sterol biosynthetic gene networks, may represent biomarkers or molecular targets for intervention in PMD.

(SYMP24) Estradiol, steroid-regulated genes, brain function and behavior: of mice and women

Variations in sex-steroid regulated genes: ovarian steroid hormones modulate working-memory related brain function in women

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Regulatory actions of ovarian steroids on genes relevant to brain function are well-documented. Here, we employed a hormone-manipulation paradigm to test for interactions between ovarian hormones and specific sex steroid-regulated genes on brain function. Working memory-related regional cerebral blood flow (rCBF) and BOLD signal change were measured with H215O-PET and fMRI, respectively, in healthy women during three pharmacologically-controlled hormone conditions: GnRH agonist-induced ovarian suppression, estradiol addback, and progesterone addback. For each of the three hormone conditions, a discovery dataset was obtained with rCBF PET in 39 women genotyped for BDNF Val66Met and COMT Val158Met, and for BDNF genotype, a confirmatory dataset was obtained with fMRI in 27 women.

A hormone-by-BDNF interaction was observed on working memory-related hippocampal function (PET: $F_{2,37}=9.11$, $p=0.05$ SVC for FWE; fMRI: $F_{2,26}=5.43$, $p=0.02$ uncorrected): there was atypical hippocampal recruitment in Met-carriers but only in the presence of estradiol. Additionally, a hormone-by-COMT interaction was found in the right dorsolateral prefrontal cortex ([DLPFC]; PET: $F_{2,68}=9.34$, $p=0.00026$): during estradiol only, a COMT genotype dose-related, step-wise DLPFC activation pattern was observed: Met homozygotes had the highest activation, followed by heterozygotes and then Val homozygotes.

The fact that the BDNF-by-estradiol interaction was present in the hippocampus and not the DLPFC, whereas the COMT-by-estradiol interaction was present in the DLPFC and not the hippocampus suggests regional specificity that reflects where in the brain these genes have particular functional relevance. These findings also suggest that genomic variation in sex steroid-regulated genes could contribute to the differential behavioral sensitivity to estradiol in some women.

(SYMP25) The physiopathological significance of neuroactive steroid synthesis and metabolism

Neurosteroid regulation of lipid phenotype in ApoE3 and ApoE4 carriers

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Context

Allopregnanolone (Allo) is an endogenous neurosteroid currently being developed as a first-in-class regenerative therapy for late onset Alzheimer's disease. Our previous IND-enabling preclinical studies demonstrated therapeutic efficacy of Allo to promote neurogenesis, reduce brain -amyloid load and restore cognitive function.

Objective

To establish feasibility of a precision medicine approach for Allo treatment.

Methods

We evaluated hippocampal nuclear and mitochondrial transcriptomic profiles, MRI-based ROI grey and white matter structure and memory function in both male and female humanized APOE3 and APOE4 mice.
Treatment: 6 months of a Allo treatment in a regenerative treatment regimen.

Results

Outcomes of these analyses indicate that Allo modification of hippocampal nuclear gene transcriptional profile was highly influenced by chromosomal sex and APOE genotype. Changes in nuclear gene expression profile were consistent with Allo mechanisms of action to promote regenerative, reduce inflammation and mitochondrial function. Allo dramatically increased expression of mitochondrial encoded genes in both APOE 3/3 and 4/4 males and females. Gray matter volume in multiple brain regions was significantly increased in female APOE4 carriers. Fractional anisotropy was significantly increased by Allo in multiple white matter tracks. Functional assessment indicated that Allo significantly improved memory function in APOE4/4 male and female mice.

Conclusions

Results of Allo treatment indicate a sustained impact of Allo evident one week post last treatment, that Allo regulation of nuclear gene expression is strongly influenced by chromosomal sex and APOE genotype and that Allo promotes mitochondrial gene expression in both male and female APOE4 carriers. These preclinical data are consistent with exploratory outcomes in a Phase 1 clinical trial of Allo in persons with Alzheimer's disease. Collectively, these preclinical and clinical data provide evidence in support of a precision medicine approach to Allo clinical trial design that targets APOE4 carriers which is currently advancing to a Phase 2 clinical trial of Allo in persons with mild Alzheimer's disease.
This work was supported by National Institute on Aging grants P01-AG026572, U01 AG031115, U01 AG047222, 1R01AG063826 to RDB.

(SYMP25) The physiopathological significance of neuroactive steroid synthesis and metabolism

Sex dimorphic neurosteroidogenesis: physiopathological role

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It is now clear that nervous system is a steroidogenic tissue. Indeed, molecules involved in the synthesis and metabolism of steroids, such as steroidogenic acute regulatory protein, translocator protein 18kDa, cytochrome P450 cholesterol side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, 5α-reductase, 3α- and 3β-hydroxysteroid oxidoreductase and aromatase, have been demonstrated to be expressed in the central and peripheral nervous system (Melcangi et al, Cell Mol Life Sci. 2008, 65:777-97; Giatti et al., Prog Neurobiol 2019, 176:1-17).
Sex dimorphic features have been reported in the synthesis as well as in the levels of neuroactive steroids (Giatti et al., Prog Neurobiol 2019, 176:1-17). Neuroactive steroid family includes steroid hormones coming from peripheral glands and steroids directly synthesized in the nervous system (i.e., neurosteroids). It is interesting to highlight that these two pools of steroids interact each other. Thus, nervous system adapts its local levels of neuroactive steroids in response to changes in gonadal hormones (Caruso et al., J. Neuroendocrinol. 2010, 22:1137-1147). This response is sex and regional specific and depends on the duration of the peripheral modifications. In addition, the levels of neuroactive steroids in control animals are different: a) between peripheral and central nervous system (CNS), b) among CNS areas, c) between plasma, cerebrospinal fluid and nervous system and d) between the two sexes (Caruso et al., Psychoneuroendocrinology 2013, 38:2278-2290). Many neuropathological disorders show sex differences in their incidence, symptomatology and/or neurodegenerative outcome. In agreement, as demonstrated in different experimental models of neurodegenerative and psychiatric disorders, levels and synthesis of neuroactive steroids are affected by the pathology and the sex (Giatti et al., Front Neuroendocrinol 2019, doi: 10.1016/j.yfrne.2019.100804). Altogether, these observations might provide the basis to design sex-specific neuroprotective therapies based on neuroactive steroids.

(SYMP26) Neurosteroids and neurogenesis and aging brain

Identifying Alzheimer's risk at menopause: therapeutic opportunities to prevent or delay Alzheimer's

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Context

Women are at a 2-fold greater risk of developing Alzheimer's disease. Identification of mid-life indicators of risk provide a clinical opportunity to prevent late-life neurodegenerative disease.

Objective

To determine midlife indicators in the female predictive of late-life neurodegenerative disease risk.

Methods

We examined the predictive validity of clinically deployable indicators of metabolic and cardiac health in postmenopausal women from the Early versus Late Intervention Trial with Estradiol (n = 497). Based on nine metabolic biomarkers (fasting blood glucose, insulin sensitivity, ketones, triglycerides, high-density lipoprotein, low-density lipoprotein, hemoglobin A1c, and blood pressure), K-means clustering categorized women into three distinct phenotypes: healthy, high blood pressure, and poor metabolic. ApoE4 genotype was classified as either ApoE4+ or ApoE4-. Measures of global cognition, executive functions, and verbal memory, were collected

Results

Among clinically healthy postmenopausal women, nine metabolic biomarkers (fasting blood glucose, insulin sensitivity, ketones, triglycerides, high-density lipoprotein, low-density lipoprotein, hemoglobin A1c, and blood pressure), K-means clustering categorized women into three distinct phenotypes: healthy, high blood pressure, and poor metabolic. In ApoE4- women, CIMT was significantly lower in those classified as healthy compared with high blood pressure phenotype ($p = 0.004$). In ApoE4+ women, CIMT was significantly higher in those with poor metabolic phenotype compared with healthy ($p = 0.0003$) and high blood pressure ($p = 0.001$) phenotypes. In the total sample of 497 women, verbal memory was lower in the poor metabolic cluster ($P=0.04$). Among ApoE4+ women, performance in all cognitive domains was lowest in the poor metabolic cluster. Differences in executive functions among metabolic clusters were detected only in ApoE4+ women (P value for interaction=0.003).

Conclusions

In a general population of clinically healthy postmenopausal women, ApoE4+ women with a poor metabolic profile were more likely to have higher levels of subclinical atherosclerosis compared with ApoE4+ women with healthy metabolic profile and ApoE4- women. Further, ApoE4+ women with poor metabolic profile has significant cognitive decline relative to metabolically healthy women. These data indicate a window of opportunity for interventions to reverse the trajectory of the preclinical phase of Alzheimer's disease.

This study was registered in ClinicalTrials.gov as trial number NCT00114517 and supported by NIH R01AG024154 to HH and National Institute on Aging grants P01-AG026572, R01AG057931 and R37AG053589 to RDB.

(SYMP26) Neurosteroids and neurogenesis and aging brain

Protective effects of estrogens in the aging brain

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In contrast to much of the basic science literature, clinical studies provide mixed findings regarding the effects of estrogens on the aging brain in women. Menopausal hormone therapy (MHT) has mixed effects on clinical endpoints of cognition and Alzheimer's disease (AD), and findings regarding estrogen alone frequently differ from those of estrogen plus progestogen. For example, an analysis of all-cause mortality over 18 years of follow-up in the Women's Health Initiative (WHI) revealed positive findings of estrogen and brain aging; conjugated equine estrogen (CEE) reduced risk of death from AD by 26%. Notably, that effect was driven by women who were age 70-79 years when they initiated treatment in the WHI. That result contrasts with the timing hypothesis because it was the older women – not the younger women who benefited from CEE. Further evidence of benefit with CEE comes from a meta-analyses of observational studies showing a 29% reduced risk of AD among women with a history of MHT use, commonly of estrogen alone and typically of CEE alone. Thus the recent WHI data and meta-analyses are in agreement that CEE may confer benefit to the aging brain. In contrast, there is no strong evidence of benefit for combined estrogen plus progesterone on the aging brain. Four larger randomized, placebo-controlled trials show neutral effects of MHT, including CEE plus medroxyprogesterone acetate (CEE/MPA), on cognitive test performance in early postmenopausal women. Evidence harm with CEE/MPA comes from the original publication from the WHI Memory Study (WHIMS) showing a doubling of dementia incidence in women aged 65 years and older after 5 years of treatment with CEE/MPA. Interestingly, those WHIMS findings contrast with the newer 18-year follow-up data which show no increased risk of death from AD with CEE/MPA. Together these studies suggest a possible early period of vulnerability to dementia with this particular formulation of MHT. Overall, MHT is not recommended for primary prevention of AD or treatment of cognitive dysfunction. The effects of MHT on cognition in women with bothersome vasomotor symptoms are unknown but evidence links VMS with memory dysfunction, suggesting potential benefit for those women.

(SYMP26) Neurosteroids and neurogenesis and aging brain

Nestorone and myelin regeneration

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Progesterone (P) is synthesized locally in the CNS where it appears to play a role in developmental myelination. In addition, treatment with P reduces demyelinating lesions in experimental autoimmune encephalomyelitis (EAE). These studies suggested that a synthetic progestin with chemical structure similar to that of P may have beneficial pleiotropic effects in the brain. Nestorone [(NES) also known as segesterone acetate; a derivative of 19-norprogesterone] is a synthetic, non-androgenic progestin. NES is 100 times more potent than P, with high selectivity for progesterone receptors that does not transactivate the androgen receptor.
We showed that NES was able to stimulate oligodendrocytes and myelin repair in both *in vitro* and *in vivo* experiments. In addition, NES was able to decrease the severity of the disease induced in the Experimental Autoimmune Encephalomyelitis (EAE) mouse model for multiple sclerosis (MS). The remyelinating effect of P and NES were mediated via progesterone receptors (PR) and NES showed consistent positive responses in the same dose range.
An effective treatment strategy for MS should include myelin regenerative agents as an adjuvant therapy to disease modifying agents, in order to reverse axon demyelination and prevent irreversible axon loss. This is currently a major missing piece in MS therapy. NES‘s myelin regenerative action may be a strategy to advance the development of a new treatment option to remyelinate axons in MS patients. In addition, understanding the neuroprotective and remyelinating effects of NES will also advance research to promote neuroregeneration more broadly and could lead to development of possible therapies for other neurodegenerative disorders and demyelinating diseases.

(SYMP27) Sleep disorders in women

Sleep and sexual function: is there a connection?

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Sleep disturbances are prevalent in the general population, are more common in women, and increase with advancing age. Midlife women, in particular, commonly experience sleep disturbances with nearly half of women reporting insomnia during the menopause transition. Sexual dysfunction is also highly prevalent in women with 43% reporting a sexual health concern and 22% experiencing a sexual problem associated with personal distress. Poor sleep and sexual dysfunction are independently associated with reduced quality of life and poorer physical and emotional health, and both have a number of biopsychosocial determinants. Sleep disturbances, including obstructive sleep apnea, insomnia, poor sleep quality and daytime sleepiness, and sexual dysfunction have been linked in both pre- and postmenopausal women. Whether there is a shared mechanistic pathway or these associations can be explained on the basis of factors which contribute to both sexual dysfunction and poor sleep remains unclear. There are a variety of determinants influencing both sleep and sexual function in women, including age, physical and emotional health, sociocultural factors, reproductive and hormonal status and medication use. Additional investigation is needed to better understand potential direct and indirect links between sleep disturbances and female sexual dysfunction. Nonetheless, existing studies support the importance of sufficient and high-quality sleep for maintenance of sexual function in women.

(SYMP29) VVA/GSM and regenerative gynecology

Vaginal health insights views & attitudes in LATAM

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In postmenopausal women, estrogen deficiency can lead to vaginal atrophy, presenting symptoms of loss of vaginal lubrication, vaginal discomfort, itching, burning and pain. Vaginal atrophy can adversely affect sexual health and quality of life. Half of postmenopausal women experience symptoms attributable to the condition, but they may not appreciate the impact of these and be unaware that effective treatment is available. Previous studies (Climacteric 2012; 15: 36–44; Menopause 2013; 20: 1043–8; Menopause Int 2013; 19: 20–7) on vaginal health, involving postmenopausal women from seven countries in Europe and North America, showed that women generally had little knowledge of vaginal atrophy. Sociocultural factors made a substantial difference to the way the condition was perceived by women, its effect on relationships, and the nature of the support available from healthcare teams. In another study (Climacteric, 2018; 21:397-403), postmenopausal women, from Latin America, over half (57%) reported experiencing symptoms of vaginal atrophy and 6% attributed symptoms of vaginal atrophy directly to the condition. The 71% of women did not consider the condition to be chronic, resulting in many of them not accessing effective therapy. Half the women (49%) affected by vaginal atrophy had used lubricating gels and creams. The 36% of women had used some form of local hormone treatment. To understand symptoms and/or treatment options for vaginal discomfort, the majority of participants (92%) were willing to seek advice from healthcare professionals. Most (61%) would feel comfortable talking to their doctor about this. In conclusion, many postmenopausal women in Latin America lack knowledge of postmenopausal vaginal atrophy, not appreciating the chronic nature of the condition, and may benefit from dialog initiated by healthcare professionals to facilitate greater understanding and increased awareness of the availability of effective treatment. It was recommended that medical practitioners should proactively initiate discussions with patients, to improve understanding of the condition and raise awareness of treatment options.

(SYMP29) VVA/GSM and regenerative gynecology

Local estrogen for treatment of vulvovaginal atrophy in women with breast cancer receiving aromatase inhibitors

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Women with breast cancer treated with aromatase inhibitors frequently suffer from symptoms of vaginal atrophy. Local estrogens relieve vaginal problems but the safety in these women must be confirmed. The aim of the present multi-center study was to assess the efficacy and safety of ultra-low dose 0.005% estriol vaginal gel in women with breast cancer receiving non-steroidal aromatase inhibitors and experiencing moderate to severe treatment-related vulvovaginal symptoms and signs. Sixty-one postmenopausal women with hormone receptor-positive early breast cancer receiving aromatase inhibitors were randomized to either estriol vaginal gel (n=50) or placebo (n=11) for 12 weeks. Symptoms and signs of vulvovaginal atrophy were assessed at baseline and at weeks 3 and 12; sexual functioning was also evaluated using the Female Sexual Functioning Index questionnaire (FSFI), as well as circulating estrogens, FSH and LH. Active treatment significantly improved maturation value and pH, vaginal dryness and global scores of symptoms and signsof vulvovaginal atrophy in comparison with placebo. Active treatment also increased the total FSFI score and most of the FSFI domains, although not significant compared to placebo. Small oscillations were observed in FSH and LH, which remained within the postmenopausal range, and were not significantly changed from baseline to week 12. Estriol levels increased initially and normalized by week 12, and estradiol and estrone remained mostly undetectable throughout the study. These findings confirm the efficacy of 0.005% estriol vaginal gel in women with breast cancer receiving aromatase inhibitors and suffering from bothersome vaginal symptoms. Furthermore, the transitory absorption of estriol in initial weeks and a non-significant variation of FSH after 12 weeks of treatment provide confidence for the safe use of 0.005% estriol vaginal gel in women with breast cancer affected by bothersome vaginal symptoms.

(SYMP29) VVA/GSM and regenerative gynecology

Should we talk about cosmetic gynecology or it is regenerative gynecology

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Cosmetics are substances that you put on your face or body that are intended to improve your appearance (Cambridge dictionary). The word "cosmetic" derives from the Greek κοσμητικὴ τέχνη (kosmetikē tekhnē), meaning "technique of dress and ornament", from κοσμητικός (kosmētikos), "skilled in ordering or arranging" and that from κόσμος (kosmos), meaning amongst others "order" and "ornament" (Wikipedia). Regenerative is the process of improving a place or system, especially to make it more active or successful (Cambridge dictionary) Regenerative. Regenerative in medicine is a branch of translational research in tissue engineering and molecular biology which deals with the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function" (Wikipedia).
The primary goal when treating vulvo vaginal atrophy is to relieve symptoms. Currently available treatment options include long-acting vaginal moisturizers, systemic hormonal therapies, low-dose vaginal estrogen therapies (e.g., vaginal creams, intravaginal tablets, or intravaginal rings) and intravaginal prasterone. For women with vulvovaginal symptoms, first-line therapies include long-acting vaginal moisturizers, low-dose vaginal estrogens, or intravaginal prasterone. Emerging treatments include ospemifene, a SERM with specific vaginal function and heat energy based treatments, such as vulvo-vaginal laser, which are being studied in this area.
All the different treatments decrease vaginal pH, some of them has properties like preservation of water equilibrium; others increase collagen fivers, neovascularization, gross vaginal mucosae and vaginal lactobacilli. Given the mechanisms of action of the different treatments and the definitions of the two concepts, we can conclude that we must talk about regenerative gynecology when we talk about VVA treatments.

(SYMP31) Osteoporosis and intervertebral disk

Connective tissue and intervertebral disc changes with the menopause and treatment

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The impact of menopause and HRT on bone density and the incidence of osteoporosis is well established. Less so, is their role in other connective tissue systems, although the skin and blood vessels have been studied.
The association between the menopause, various postmenopausal treatments and the intervertebral discs has been attracting attention.
A number of publications have appeared and there is more work in progress.
Baron Y, Brincat et al, and Gambacciani M had established a 30% drop intervertebral disc height after the menopause, in two separate publications, with change with treatment.
Stevenson & Stevenson et al had showed in a prospective study that postmenopausal women lumbar disc height responded in a close related fashion, to 1 mg and 2mg of 17β oestradiol.
Our Unit Baron, Brincat, Pollacco et al has shown that postmenopausal osteoporotic women had the thinnest intervertebral discs of all. They confirmed that postmenopausal women had thinner intervertebral discs then premenopausal ones. Also in a cross sectional study we are able to demonstrate that with adequate oestrogen replacement the intervertebral heights were preserved to pre-menopausal levels. This was not necessarily so when other methods commonly used in the menopause were looked at. This included the bisphosphonates and calcium supplements.

Conclusion

Intervertebral discs provide the necessary cushioning to reduce vertebral osteoporotic fracture. They are also responsible for 20% of the spinal height.
The menopause has a profound effect on the integrity of the intervertebral discs and adequate HRT(RRT) is the best way for retaining that integrity.

(SYMP31) Osteoporosis and intervertebral disk

Optimal screening for osteoporosis: when and how

Tobias De Villiers (ZA)
Stellenbosch University

Osteoporosis and associated fractures are common in women after midlife and will increase as the population ages. Osteoporosis-related fractures cause a significant increase in morbidity and mortality. It decreases the quality of life and productivity of many older women with an increasing burden on health care resources. Future risk of fracture can be reduced by evidence –based interventions. This entails both lifestyle-interventions as well as pharmacological treatment. It is thus an attractive proposition to estimate the future risk of fracture in all women at the age of 50 years or at menopause, whichever occurs first in order to identify the population at highest risk of fracture. This can be achieved in a non-invasive fashion by targeted clinical history taking. The future risk of fracture can be quantified using computerized models that integrate all risk factors, with or without dual x-ray absorptiometry. Individuals found to be at increased risk of fracture need also to be assessed by dual energy x-ray absorptiometry and in the absence of lateral vertebral assessment, also by conventional X-ray imaging. All women should be screened by dual X-ray absorptiometry at the age of 65 years, if not done before that time. At the age of 50, all women should be informed of a bone-friendly lifestyle. Pharmacological intervention should be reserved for those women at an appropriately high risk of future fracture.

(SYMP31) Osteoporosis and intervertebral disk

Postmenopausal osteoporosis. Is it a marker for other diseases?

Martin Birkhaeuser (CH)
University of Berne, Switzerland

If osteopenia or osteoporosis is discovered in postmenopausal women, the main cause is not always the decreased estrogen production occurring in menopausal transition. Differential diagnosis should include the following items:

1. General risks, behavior, including family high-risk, actual or former malnutrition, episodes of anorexia nervosa, immobility, Vitamin D and/or calcium deficiency and heavy smoking.
2. Gynaecological-endocrinological factors, such as primary and secondary amenorrhea, early menopause, hysterectomy with and without bilateral ovariectomy, athletic triad, hyperprolactinemia and the regular intake of suppressors of the ovarian axis (e.g. GnRH-analogs or depot-MPA). Finally, low-dose- and ultra-low-dose combined oral contraceptives used in adolescence have to be discussed.
3. Chronic intake of specific medications, such as glucocorticoids, aromatase inhibitors, glitazones, proton pump Inhibitors or antiepileptics
4. Endocrinopathies, such as primary hyperparathyroidism, Cushing syndrome, hypopituitarism, diabetes mellitus type 1 and type 2
5. Rheumatic diseases, such as rheumatoid arthritis, autoimmune diseases
6. Gastroenterological diseases: Celiac disease, chronic inflammatory bowel disease
7. Other severe chronic diseases, such as heart failure

Finally, in presence of osteoporosis and vasomotor symptoms (VMV), a higher risk for other pathologies associated with VMS has to be considered. Coronary heart disease and depression are the most important non-osteological diseases belonging to this group. In conclusion, other non-menopausal causes of osteoporosis have always to be considered in elderly women in whom a low Bone Mineral Density (BMD) has been detected. A correct diagnosis is essential for offering the optimal treatment needed for each specific pathology.

(SYMP33) Surgery

What is the place of surgery in deep endometriosis in infertile and pelvic pain patients?

Michelle Nisolle (BE)
University of Liege

According to ESHRE recommendations of 2014, patients with pelvic pain associated to infertility would require surgical treatment but there is no evidence to perform deep endometriosis (DE) excision before IVF in infertile women in order to improve reproductive outcomes. Nevertheless, new data have been recently published in the literature and the aim of the presentation is to demonstrate the advantages of DE surgery on infertility. In 2015, Roman et al described a high rate of post-operative spontaneous conception after colorectal surgery, suggesting that complex surgical procedures do not impair fertility outcomes. In the study of the same authors published in 2018, they suggested that surgery could be considered as a first-line approach in patients with DE infiltrating the rectum and pregnancy desire. Faster conception was observed in patients receiving advice from experienced surgeons on conception modes.

In the literature, there are no RCTs comparing surgery of DE followed by IVF versus IVF in patients with deep endometriotic lesions. In the prospective but not randomized study of Bianchi et al, a positive impact of DE was significantly reported on IVF outcomes. On the contrary, in the retrospective study of Mounsambote et al, the cumulative pregnancy rate was similar in the group of patients who underwent DE surgery without bowel involvement followed by IVF (40%) when compared to the patients undergoing directly IVF (41%) after 3 cycles. Recently, in a retrospective study of 110 women, Bendifallah et al observed a positive impact of surgery in IVF outcomes, in terms of cumulative live birth rate. Even if surgery is performed after 2 IVF failures, the benefits have been described by Breteau et al. Indeed a postoperative pregnancy rate is observed in 43.8% and in 22% of them, the pregnancy has been obtained spontaneously.

As surgical procedures for eradication of DE are complex and associated to severe complications, there are usually avoided in infertile patients. In a series of 900 women undergoing surgery for colorectal involvement, Ferrier et al described severe complications occurring in 48 of them. Nevertheless, pregnancy was noted in 20 women, spontaneously in 16 women and following IVF in 4 women.

In conclusion, the choice of first line treatment, surgery or IVF, has to be taken according to the degree of pelvic pain associated to infertility, the age of the patient, the tubal permeability, the ovarian reserve and the sperm characteristics.

(SYMP34) Ethical issues in reproduction

Ethics in medical publishing

James Pickar (US)
Columbia University Medical Center

Spin the "use of specific reporting strategies, from whatever motive, to highlight that the experimental treatment is beneficial, despite a statistically nonsignificant difference for the primary outcome, or to distract the reader from statistically nonsignificant results".[1] It comes as no surprise that the majority of the time most physicians only read the abstract of an article. Based on a study of RCTs published between 2012 and 2017, in the abstracts, spin was found in 21% of results and 49.1% of conclusions.[1] The authors reported "Spin was most commonly associated with public funding." Another study compared protocols approved for funding by the Canadian IHR with reports of the trials in journal publications. Based on 48 randomized trials associated with 68 publications and 1402 outcomes, a median of 31% of efficacy outcomes and 59% of harm outcomes, per trial were incompletely reported. Additionally, "Primary outcomes differed between protocols and publications for 40% of the trials." The authors concluded that "Selective reporting of outcomes frequently occurs in publications of high-quality government funded trials.[2] Based on a literature review of RCTs of head and neck cancer treatments it was reported that "Government-sponsored trials were twice as likely to report positive results than those without government support" and "Industry-sponsored studies were about as equally likely to present positive results as studies without industry support." Those authors concluded that "our findings also indicate that the potential for bias toward publishing positive results is not necessarily limited to studies funded by industry, but may be seen with government sponsorship as well."[3] It has been suggested that "even if personal financial gain was not at stake, the pursuit of maintaining career opportunities and academic advancement could lead to publishing findings in a favorable light, thereby enhancing professional reputation and opportunities for future government and industry grant support."[3,4] The time is overdue for authors to report public funding (such as government agencies, charitable foundations or academic institutions) on conflicts of interest statements. 1. Jellison S, Roberts W, Bowers A, et al. Evaluation of spin in abstracts of papers in psychiatry and psychology journals. Epub ahead of print: Aug 5, 2019. Doi:10.1136/bmjebm-2019-111176. 2. Chan A-W, Krleža-Jerić K, Schmid I, et al. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ 2004;171(7):735-740. 3. Sun GH, Houlton JJ, MacEachern MP, et al. Influence of study sponsorship on head and neck cancer randomized trial results. Head & Neck 2013;35:1515-1520. 4. Levinsky NG. Nonfinancial Conflicts of Interest in Research. N Eng J Med 2002;347(10):759-761.

Meet the Experts

(MTE01) Stress

Reproductive consequences of stress – more than anovulation

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University of Utah

Stressful situations modify energy intake and expenditure and may provoke either weight loss or gain depending on the amount and type of fuel available, genotype, and individual behavioral responses. Stress may elicit either orexia or anorexia. To better understand mechanisms mediating stress-induced infertility, we developed a monkey model of social subordination that caused anovulation in association with altered food intake and food preferences. When high-fat, high-sugar food was plentiful, subordinated female monkeys ate more than dominant female monkeys. To the extent that social subordination in monkeys and low socioeconomic status in humans are analogous, our monkey model explains in part why obesity tracks with low socioeconomic status in humans. In contrast, in monkeys, energy deficiency elicited by undernutrition combined with increased energy expenditure synergized with social stress to compromise ovulatory function. Similarly, in women, energy expenditure acutely amplified hypercortisolism more in those with functional hypothalamic amenorrhea (FHA) than in eumenorrheic, ovulatory women. While FHA reported attitudes such as perfectionism and high drive for thinness that curb eating, attitudes associated with overeating remain to be better characterized. We posit that obesity and stress are linked because the neurobiologic reward of overeating partially constrains hypercortisolism. The reproductive consequences of energy deficiency and excess are distinct. Stressful circumstances may elicit the classical constellation of hypothalamic hypercortisolism, hypothalamic hypothyroidism, and secondary hypothalamic hypogonadism regardless of energy deficit or surplus. Importantly, both undernutrition and overnutrition reflect behavioral responses to stressful conditions. Overnutrition is more likely when there is an abundance of highly palatable (high fat, high carbohydrate) foods whereas undernutrition in women appears to reflect excessive cognitive restraint as a coping strategy. Interventions to promote better fertility and maternal-fetal health must recognize the panoply of human adaptive responses, and their respective psychoneuroendocrine concomitants, to a variety of stressful conditions. Cognitive interventions that foster better coping mechanisms not only foster fertility but also better health in offspring and maternal longevity. The health consequences of the various subtypes of FHA remain to be more explicitly delineated, but given that hypercortisolism elicits a panoply of consequences, including antagonism of estrogen and insulin action, the health consequences of FHA extent beyond reproduction compromise and include compromise of cardiovascular, brain / mental, bone, and metabolic health. Clinical guidelines must reflect the multiple manifestations of chronic stress.

(MTE04) Vitamin D

The Vit. D story in reproductive medicine. Seperating the chaff from the wheat

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University of Malta. Dept of O&G

The story of the role of Vitamin D has been around for several years but has been hampered by a number of problems. The first was a misunderstanding in the nomenclature of the 'vitamin'. It is almost wholly synthesised in the subcutaneous part of the skin from cholesterol and only 10% is obtained from dietary sources. Cholesterol is the basic molecule for many other steroid hormones including many of the sex steroids. Therefore Vitamin D should be more accurately classified as a hormone (Kiniska et al., 2008; Anagonistis et al., 2013).

The second problem was the issue of an accurate way for measuring serum levels of the vitamin/hormone and the establishment of a normal range. This has now been resolved with the normal range established by the ASEM and between 30-100micromoles/ml, with the ideal present osteoporosis at 50 micromoles/ml.

Lastly the role of calcium levels, and calcium supplementation needed to be established. Calcium only plays a role in for example preventing osteoporosis, or was it only Vitamin D supplementation. Recently a publication indicated that both Vit D and calcium were taken together were essential (Boonen S. et al., 2005). Furthermore, the debate on the actual doses of supplementation needed continues with the general consensus favouring higher doses of Vitamin D_3 supplementation, now easily with serum levels, and with calcium supplementation remaining at 1000 to 1500 mgs daily.

The role of Vitamin D in reproductive medicine is therefore still emerging since several of the previous studies, particularly those in post-menopausal

osteoporosis were undisclosed or incorrect or no continuation studies with the necessary calcium levels/supplementation were carried out.

Nevertheless, both in obstetrics as well as in gynaecological endocrinology and infertility the role for correct Vitamin D_3 supplementation is emerging. In reproductive endocrinology and infertility, a role for Vitamin D is being increasingly identified, in the aetiology and management of endometriosis (Abbas et al., 2013), PCO, recurrent miscarriage, in failed implantation as well as for good quality production of oocytes and sperm (De Leo V., Cappelli V. et al., 2018).

In Obstetrics, likewise an increased understanding is emerging on the role of Vitamin D_3 in implantation, premature labour, small for dates babies, and pre- eclampsia amongst others (Aghafari et al., 2013).

An increasing understanding in the physiology of the highly conserved hormone in evolution, with its multi systemic role at cellular level will greatly enhance its correct use in the various conditions in reproductive medicine for which it is being considered of increasing importance.

(MTE04) Vitamin D

Vitamin D supplementation after the menopause: which dosage?

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Nucleated cells have specific receptors for vitamin D that are sensitive to its endogenous status. Therefore, practically all organs or systems are sensible to hypovitaminosis D. Nevertheless, in many instances causal relationships have not been demonstrated between hypovitaminosis D and clinical or analytical findings. Most of the confusion regarding to treat or not to treat hypovitaminosis is related to the inappropriate mix of research with different rank and quality of evidence. Another issue that has caused conflictive positions is the fact that vitamin D requirements may not necessarily be similar in a given tissue or cell type in order to maintain different functions. In addition, latitude and season period of the year may increase or decrease hypovitaminosis D risk. Insulin resistance and metabolic syndrome, which are very common during the second half of pregnancy, can be improved by calcidiol or calcitriol treatment. In older women (>65 years), hypovitaminosis D may be associated with significant differences in hand grip strength, lean mass and fat mass as compared to those with normal range vitamin D circulating levels. However, very high doses do not obtain better results than lower (sufficient) supplement doses.

(MTE05) HPV

Extending human papillomavirus (HPV) vaccination beyond adolescents and after treatment for high grade CIN

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Università degli Studi di Palermo

Human PapillomaVirus (HPV) vaccination has been introduced in recent years in clinical practice as the most effective primary prevention strategy for cervical cancer and HPV-induced lesions, either benign and pre-malignant. Since its introduction, HPV vaccination has been progressively demonstrated as extremely effective in preventing extra-genital and male diseases also; furthermore, not only adolescents but also adult subjects have been investigated and reported as positively responding to vaccine immunostimulation. More recently, effectiveness of post-treatment vaccine administration has been preliminarily investigated with very promising results in terms of recurrences decrease. On these basis, we report an italian-focused picture of the state of the art and take position in favour of the extension of HPV vaccination to male adolescents, to older age groups and to treated subjects.

(MTE06) Management of preterm labor

A uterine pacemaker against preterm labor

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Preterm labor (PTL, 24-36 weeks gestation) and delivery remains one of the gravest problems in medicine today. Of the ~13 million births annually 5-10 % will be pre-term with gestational age-related myriad and lifelong neonatal complications. In industrial countries the cost of the first year of life for a premature infant is ten-fold that of a term infant. The human and monetary costs of the life-long care of affected newborns are incalculable.
The preventative use of progestins against PTL fails much of the time. Tocolytic agents that are in use against PTL are not safe and may only furnish time to treat lung maturation; effects on other organs' condition are not well studied. Generally, the intraventricular hemorrhage rate of tocolytic-treated newborns exceeds that of untreated prematures.
Electrical inhibition (EI) of muscular activity is increasingly utilized in medicine. Exposure to a briefly administered small current hyperpolarizes/depolarizes the muscle, rendering it temporarily refractory to succeeding currents. In the case of PTL this breaks the wave of excitation from adjacent uterine muscle fibers. Our successful preliminary results using EI against PTL are described.
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(MTE07) POI

Adrenal ageing in premature ovarian isufficency

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Premature ovarian insufficiency (PAI is characterized by hypergonadotropic ameno/oligomenorrhoea in women younger than 40 years of age, estradiol<50 pmol/L and FSH >40 (or 25). Hypoestrogenism directly decreases adaptive immune response. PAI, Addison's deisease and Hashimoto thyreoiditis are defined as pluriglandular autoimmune syndrome type II. Naïve CD4+T cells, upon encountering their cognate antigens presented on professional antigens presenting cells differentiate into effector cells (T helper 1;2;17;Treg) characterized by cytokine production and immune regulatory function changes. Adrenal aging in all women is characterized with dehydroepiandrosterone and its slufate decrease. In 1939. Butenandt received a Nobel prize for identifying and isolation of DHEA. Peak od DHEA values is at age of 15-19 years. Cortisol levels are increasing during aging, while DHEAS is decreasing. In focus of our interest was adrenal aging in POI patients with no autoimmune diseases, "idiopathic " POI prior to therapy.

SUBJECTS

We recruited 1300 POI patients and devided them in three groups depending on age: I 20-30 years (0.5%), II 31-35 (32%); III 36-40 (67%). Body mass index, testosterone, DHEAS and cortisol were detected in all of them by RIA.

RESULTS

BMI (I:II:III group): 19.2 + 2.1 vs. 22.8+2.0 vs. 29.5+3.2 kg/m^2); DHEAS: 2.8+0.9 vs 1.7+ 0.3: vs.2.6+ 0.7 umol/L; testosterone: 1.3+ 0.4 vs. 0.8+ 0.2 vs. 0.7+ 0.3 nmol/L; cortisol: 367.5+ 96.4 vs. 394.2+ 72.4 vs. 462.0+ 121.3 nmol/L.
BMI and cortisol were increasing from 20-40 years og age, while testosterone and DHEAS decreasing not significantly.

CONCLUSION

POI, as a stress, has to be diagnosed on time in order to prevent diseases and improve quality of life.

(MTE09) Ovarian hormones impact on somatic and mental aging

Psychiatric diseases and risk of gynecologic surgery

Liliana Gazzuola Rocca (US)
Mayo Clinic

Context
Bilateral oophorectomy has commonly been performed in conjunction with hysterectomy even in women without a clear ovarian indication; however, oophorectomy may have long-term deleterious consequences.

Objective
We studied 8 mental health conditions diagnosed before bilateral oophorectomy performed for nonmalignant indications.

Methods
We identified 1,653 premenopausal women who underwent bilateral oophorectomy for a nonmalignant indication in Olmsted County, Minnesota during the 20-year period 1988-2007. Each woman was matched by age (±1 year) to 1 population-based control woman who had not undergone bilateral oophorectomy before the index date (age range: 21-49 years). Both cases and controls were identified using the records-linkage system of the Rochester Epidemiology Project. Odds ratios (OR) and a 95% confidence intervals (95% CI) were adjusted for race, education, and income using conditional logistic regression.

Results
There was a linear trend of increasing adjusted ORs from 1.55 (95% CI, 1.31-1.83) for one mental health condition to 2.19 (95% CI, 1.40-3.41) for three or more conditions (trend P<0.001). Preexisting mood disorders, anxiety disorders, somatoform disorders, and personality disorders were associated with increased risk of bilateral oophorectomy in overall analyses. Preexisting mood disorders, anxiety disorders, and somatoform disorders were also significant in women ≤45 years of age at index date, and adjustment disorders only in women 46-49 years of age. Some of the associations were significantly different across strata by age at index date and by indication.

Conclusions
We identified several mental health conditions that were associated with bilateral oophorectomy for nonmalignant indications. Awareness of these associations may guide women and physicians in future decision-making and limit unindicated bilateral oophorectomies.

(MTE09) Ovarian hormones impact on somatic and mental aging

Loss of ovarian hormones and accelerated somatic and mental aging

Walter Rocca (US)
Mayo Clinic

Context
Bilateral oophorectomy in premenopausal women is a unique surgical procedure causing the abrupt and premature loss of ovarian hormones, primarily estrogen.

Objective
To review and summarize the growing body of literature linking loss of ovarian hormones with accelerated somatic and mental aging.

Methods
In 2016, a first biomarker study showed that the premature loss of ovarian function may lead to increased DNA methylation, a biological marker of accelerated aging (Levine et al., 2016). The finding was confirmed in 2019 by a Chinese team (Lu et al., 2019). In 2016, we showed an association between bilateral oophorectomy performed before menopause and the rate of accumulation of multi-morbidity (Rocca et al., 2016). In 2017, we addressed the cause-effect uncertainty with new analyses restricted to women who did not have any of 18 chronic conditions at baseline (Rocca et al., 2017). After adjustments for several possible confounding variables present at baseline, women who underwent bilateral oophorectomy experienced an accelerated rate of accumulation of these 18 chronic conditions considered together (Rocca et al., 2017). In addition, we reported associations of bilateral oophorectomy with long-term risk of individual conditions such as chronic kidney disease (Kattah et al., 2018) and brain imaging alterations (medial temporal lobe structural abnormalities; Zeydan et al., 2019).

Results
There is growing evidence that bilateral oophorectomy causes an alteration of several fundamental aging processes at the cellular, tissue, organ, and system levels, leading to multi-morbidity, frailty, and reduced survival. However, many questions remain unanswered.

Conclusions
Current biomarker data and clinical evidence suggests that bilateral oophorectomy is causally linked to accelerated aging, and should not be performed in women at average risk of ovarian cancer.

(MTE10) Emerging menopausal needs in cancer survivors

HRT in cancer survivors

Margaret Rees (GB)
University of Oxford

Cancer treatments can result in loss of ovarian function and, in women under the age of 45, early menopause. The management of menopausal symptoms in cancer survivors depends on their age, tumor type and stage, as well as the use of anti-estrogen therapies (for cancers considered to be hormone dependent) and concomitant morbidities. Of note for some cancers the data are limited. For non-hormone dependent childhood cancers MHT may be used until the average of the natural menopause. For gynecological cancers, MHT use depends on type and stage as some are hormone dependent and others are not. The limited data suggest that women with low-grade, early-stage endometrial cancer may consider systemic or topical estrogens. There is no evidence regarding the use of ospemifene or prasterone. For uterine sarcomas, estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether MHT can be used. The three major types of ovarian cancer are epithelial (EOC), accounting for 90% of cases, germ cell (3%), and sex cord-stromal (2%). The limited evidence available suggests that MHT, either systemic or topical, does not appear to be associated with harm and does not decrease overall or disease-free survival in women with non-serous epithelial ovarian cancer and germ cell tumors. Caution is required with both systemic and topical MHT in women with serous and granulosa cell tumors because of their hormone dependence. There is no evidence to contraindicate the use of systemic or topical MHT by women with cervical, vaginal or vulvar cancer, as these tumors are not considered to be hormone dependent. Breast cancer survivors should not generally be treated with either systemic estrogen-based MHT or tibolone. The concern is a risk of recurrence. There are no data regarding the use of ospemifene or prasterone.

(MTE11) Preeclampsia: from pathophysiology to therapy

Role of angiogenic factors in pathophysiology of preeclampsia

Tomoyuki Fujii (JP)
The University of Tokyo Graduate School of Medicine

Preeclampsia is defined as the syndrome with “Elevated blood pressure after 20 weeks of gestation (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)” and “Proteinuria (> 0.3 g/24 hours) or Evidences of multi-organ involvement including thrombocytopenia, renal dysfunction, liver dysfunction, central nervous system perturbations, or pulmonary edema.” Disease of preeclampsia has been known for many years. On the papyrus excavated from Kahun, a city of middle kingdom of Egypt B.C. 2200, it is described that “On the day of delivery, let the women bite a piece of wood, so that they do not bite their tongues.” This is surely the management for eclampsia. Many studies have been performed and many pathogenic mechanisms have been proposed. Preeclampsia is now considered to be a disease of vessels. As the pathogenic process, 2 stage theory has been proposed. At the first stage, by some causes, vascular construction of placenta is deranged and ischemia in placenta occurs. At the second stage, vasoactive substances are released from ischemic trophoblasts in placenta, and then the vasoactive substances injure systemic vascular endothelial cells, resulting in the endothelial dysfunction that can induce the signs and symptoms of preeclampsia. It has been reported that serum soluble Flt-1(sFlt-1) level is elevated in women with preeclampsia compared to the women with uneventful pregnancy. Pregnant mice with human sFlt-1 transfected gene only in placenta are reported to reveal hypertension and proteinuria during pregnancy. We have found that cultured cyto-trophoblasts (CTs) increase the production and secretion of vascular endothelial growth factor (VEGF) under the hypoxic condition as well as other kinds of cells such as human umbilical vascular endothelial cells (HUVECs) and villous fibroblasts (VFs). However, only CTs but not HUVECs nor VFs increase the production and secretion of sFlt-1 under the hypoxic condition. This suggests that under hypoxic condition, trophoblasts secret sFlt-1 but not VEGF. Thus, sFlt-1 might be one of the vasoactive substances released from ischemic placenta and injuring systemic vascular endothelial cells. In preeclampsia, hypoxic trophoblasts secret much amount of soluble Flt-1, resulting in the systemic vascular disorder, and may induce signs and symptoms of preeclampsia.

Scholarship Courses

(SCHOLARSHIP01) Scholarship-course 1

Polycystic ovary syndrome, fertility and beyond

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At an early age the most common reason of women diagnosed with PCOS to consult a doctor is irregular bleeding and infertility. Bleeding problems can often be addressed adequately by hormonal interventions. Prognosis for infertility is usually excellent with high cumulative (singleton) pregnancy rates if ovulation induction is applied prudently, and *in vitro* fertilization in used along with single embryo transfer. However, pregnancies complications (especially gestational diabetes) are distinctly increased even in singleton pregnancies. Consequently, perinatal outcomes are often compromised. Closer obstetrical monitoring seems warranted.
We now know that subtle but distinct cardiometabolic abnormalities can already be observed at an early age in both male and female off spring of women with PCOS. It is hard to assess to what extent this is due to a suboptimal early embryo development or a genetic predisposition.
When women with PCOS get older, menstrual cycle patterns often normalize, but metabolic abnormalities aggravate and type 2 diabetes or hypertension occurs. Many studies confirm the presence of subclinical cardiovascular disease (i.e. abnormal intima media thickness and flow mediated dilatation) in women with PCOS between 40 and 50 years of age. However, despite overwhelming evidence suggesting increased risk for cardiovascular disease in these women, most studies so far failed to demonstrate an increased incidence of cardiovascular events such as myocardial infarction, stroke or death. It remains surprising that many increased risk factor in PCOS for developing cardiovascular disease do not seem directly linked to actual disease.
PCOS has become a disease condition broadly recognized as having major implications for quality of life throughout the life cycle. In the past, gynecologists focused only on reproductive dysfunction in these women, but at present many other specialties are getting involved. We need multi-disciplinary approaches for proper care of women with PCOS at different phases of life.

(SCHOLARSHIP01) Scholarship-course 1

Insulin signaling and metabolic syndrome

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Gynecological Endocrinology Center, Department of Obstetrics and Gynecology, University of Modena and Reggio Emilia, Italy

Abnormal metabolism in premenopausal women is not a so frequent occurrence unless they are diabetic or probably PCOS patients. In fact the occurrence of metabolic syndrome (MS) is classically showing up in women that are overweight/obese and/or are/have been PCOS and/or have someone with diabetes in the family. The common feature of all such predisposing factor is the compensatory hyperinsulinemia.

The compensatory hyperinsulinemia, that is induced by insulin resistance (IR), is classicaly present in a high percentage of PCOS that in the same time are typically characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries.

Metabolic abnormalities such as overweight/obesity and hyperinsulinism or insulin resistance are frequent findings in PCOS patients and such impairment induce a higher production of androgens and reduced sensitivity to insulin.

It becomes important to screen PCOS whenever they come in our office so that to evaluate those subjects that have IR and impaired metabolic control so that to avoid not only the insulin-induced impairments of reproductive axis but also the abnormal effects on the vascular control that rise the cardio-vascular risks.

It becomes relevant to perform a good anamnesis and an evaluation not only of HOMA index but also the dynamic response of insulin to the glucose load. The insulin signalling is relevant in such conditions since if it is impaired (and this is the case of those patients with familial diabetes) the consequent IR triggers various physiopathological conditions that create the basis of the metabolic syndrome.

Several solutions might be proposed both on the side of treatment using the classic metformin or the integrations such as inositols and lipoic acid as well as the combination of other nutreceutic compounds such as carnitines, n-acetyl cysteine (NAC) and L-arginine (L-ARG) but the most relevant intervention remains a drastic change of life style: diet and constant physical activity are the real true “medical intervention”.

(SCHOLARSHIP01) Scholarship-course 1

Decision taking in the process of treating female infertility

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Faculty of Life Sciences, Bar Ilan University, Ramat Gan, Israel

It is essential that fertility treatment is individualized based on a thorough diagnostic work-up, with treatment tailored to the patients' requirements. This individualization should be kept in mind during the main decision points that occur before and during treatment. Treatment customization must include consideration of both the woman and her partner involved in the process together, including their collective treatment goals. Once treatment goals have been agreed and diagnostic evaluations performed, personalization based on patient characteristics, together with an understanding of treatment goals and patient preferences, enables the selection of appropriate treatments, protocols, products and their dosing. Following treatment initiation, monitoring and adaptation of product and dose can then ensure optimal outcomes. Currently, it is not possible to base treatment decisions on every characteristic of the patient and personalization is based on biomarkers that have been identified as the most relevant. However, in the future, the use of artificial intelligence coupled with continuous monitoring should enable greater individualization and improve outcomes. This review considers the current state-of-the-art related to decision points during individualized treatment of female infertility, before looking at future developments that might further assist in making individualized treatment decisions, including the use of computer-assisted decision making. 1Gynecol Endocrinol. 2019 Dec;35(12):1027-1036

(SCHOLARSHIP01) Scholarship-course 1

The functional hypothalamic amenorrhea

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Functional hypothalamic amenorrhea (FHA) is one of the most common causes of secondary amenorrhea. It is classified as hypogonadotropic hypogonadism. There are three types of FHA: weight loss-related, stress-related, and exercise-related amenorrhea. FHA results from the aberrations in pulsatile gonadotropin-releasing hormone (GnRH) secretion, which in turn causes impairment of the gonadotropins (follicle-stimulating hormone and luteinizing hormone). The final consequences are complex hormonal changes (short –and long-term) manifested by profound hypoestrogenism. One of the most important consequesnces is depressive impact on reproductive function. The most characteristic feature is anovulation. FHA exerts a negative influence on the skeletal system. It is related to a great extent to the failure to achieve peak bone mass (PBM). FHA patients are threatened by osteopenia and osteoporosis. Hypoestrogenism can interfere with the cardiovascular system function in many ways. It is refferd mainly to endothelial dysfunction and changes in lipid profile. Hypoestrogenism in young women with FHA is strongly related to changes in different neuropeptides, neurotransmitters and neuro- steroids activity at the brain level. Specifically, serotonin, dopamine and allopregnanolone fluctuations can modulate mood in FHA amenorrheic women. Sexual dysfunctions in FHA can be related to hypoestrogenism and hypoandrogenemia. FHA is important clinical problem.

(SCHOLARSHIP02) Scholarship-course 2

The luteal phase defects and early pregnancy loss

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During the luteal phase of every reproductive cycle, the uterus prepares for embryo implantation. The corpus luteum in the ovary produces progesterone during early pregnancy. Progesterone (P) is the main hormone responsible for coordinating the luteal phase via the secretory transformation of the endometrium, favouring embryo implantation and providing immunological tolerance of the implanted embryo . Early pregnancy luteectomy results in miscarriage through the loss of P support ; withdrawal of progesterone in early pregnancy typically results in a miscarriage, and anti-progesterone drugs are powerful inducers of abortion . Therefore, adequate P is required for successful pregnancy in both natural conception and assisted reproductive technology (ART) cycles. A progesterone-related problem, often given the name 'luteal phase defect' (LPD), is considered to be one of the causes of a euploid miscarriage. Progesterone is essential for maintaining the decidua, and it is hypothesized that a defect in the function of the corpus luteum can result in low progesterone levels which in turn may increase the risk of miscarriage. However, there is no clear definition for LPD and there are certainly no reliable tests to identify patients who may have the condition. Serum and salivary progesterone have been used; however, the diagnostic and prognostic value of the progesterone level has remained unclear. Furthermore, direction of causality confounds interpretation of a progesterone result, i.e., if the progesterone level is found to be low in early pregnancy, we cannot know if the low progesterone is the cause or effect of a miscarriage.

Luteal phase support (LPS) is usually given in ART cycles to optimize the chances of successful pregnancy. Although human chrorionic gonadotropin (hCG), gonadotropin releasing hormone (GnRH) agonists, or estradiol can also be used to support pregnancy, exogenous P is preferred. P can be administered vaginally, orally, rectally, subcutaneously, or intramuscularly, and natural or synthetic progestogens can be used. The optimal route of delivery, type, dose, and duration of P treatment remains under discussion. A recent Cochrane review showed that both hCG, P or addition of GnRH agonist to P seem to be associated with better pregnancy outcomes than placebo, although hCG increases ovarian hyperstimulation syndrome (OHSS) risk compared to placebo. Addition of estrogen to P has not demonstrated to confer an increase in pregnancy rates. In any case, among all the different options and combinations available, P alone remains the most used option for LPS as it combines efficiency and safety at the same time. Although there is no evidence of the perfect protocol for all patients, recent studies point to the need of individualizing luteal phase support according to the needing of each patient.

Approximately half of all miscarriages, including pregnancy losses in women with recurrent miscarriage, are due to numeric chromosome errors with trisomy being the most frequent, especially with advancing maternal age, followed by polyploidy and monosomy X.15 Such "aneuploid" miscarriages are thought to occur on a random basis, meaning that the risk of subsequent miscarriage is not increased. "Euploid" miscarriages, on the other hand, are more frequently diagnosed with increasing number of previous miscarriages. A history of previous miscarriage identifies those at risk of a future miscarriage, and the risk of a future miscarriage increases with the increasing number of previous miscarriages. The absence of a meaningful test for LPD left researchers with the challenge of not knowing which patients to target with progesterone treatment. Researchers over the past six decades responded to this challenge by targeting 'enriched' populations, in whom the overall risk of miscarriage is higher than the unselected population, and any pathology causing miscarriage, including LPD, could reasonably be expected to be more prevalent. The two key populations targeted for enrichment were women with previous recurrent miscarriages and women with early pregnancy bleeding. The first randomized trial in women with recurrent miscarriage was published in 1953, and 11 trials followed in the subsequent decades. The first trial in women with threatened miscarriage was published in 1987, and since then 7 further trials have been conducted. However, these trials used different progestogens, were small and methodologically weak, producing heterogenous and unreliable results. Policy makers have therefore been unable to make evidence-based recommendations on the use of progestogen supplementation to improve outcomes in these cohorts of women. The PROMISE and PRISM Trials are two very high quality trials that have addressed the effects of first trimester use of vaginal micronized progesterone treatment in women at risk of a miscarriage.

The dual risk factors of early pregnancy bleeding and a history of previous miscarriage identify high risk women in whom progesterone is of benefit. The increased effectiveness of progesterone with increasing number of miscarriages indicates that endometrial defects are a major driver of higher-order miscarriages.

(SCHOLARSHIP03) Scholarship-course 3

Modern evaluation of abnormal uterine bleeding

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New York University School of Medicine

Abnormal uterine bleeding in women older than age 40 years, and certainly in menopausal patients, mandates evaluation, mainly to exclude cancer and hyperplasia, but also to better diagnose the source of the bleeding to appropriately manage the patient. In the past, dilation and curettage was the mainstay of diagnosis. This gave way to in-office suction pump-generated biopsies. Most recently, disposable biopsy instruments with their own internal piston to generate suction have become the standard of care. Rarely has such a technique received such widespread acceptance with such limited validation. Transvaginal ultrasonography, when technically feasible, is a noninvasive way to image the endometrial cavity. Saline-infusion sonohysterography is a subset of transvaginal ultrasonography reserved for patients in whom an adequate endometrial echo is not seen or when an endometrial echo is seen but not sufficiently thin. Appropriate understanding and use of transvaginal ultrasonography and addition of sonohysterography when necessary can allow a clinical algorithm that can triage patients with abnormal uterine bleeding to 1) no anatomic pathology best treated expectantly; 2) a global endometrial process, in which case random blind endometrial sampling is appropriate; or 3) a focal endometrial abnormality in which case endometrial sampling should be done with the visualization offered by hysteroscopy. Newer disposable office hysteroscopes finally allow office hysteroscopy to be done as a truly "point-of-care option." Finally, the incidence of thick endometrial echo found incidentally in postmenopausal women with no bleeding is extremely high (10–17%) and should not trigger automatic invasive endometrial evaluation.

(SCHOLARSHIP04) Scholarship-course 4

The peri-menopause: risks and management

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The perimenopause, also called the menopausal transition, is a stage of decreasing secretion of ovarian estrogens. As a consequence, women present bio, psycho and social changes. Menstrual irregularities usually mark the initiation of the perimenopause. These irregularities continue until women have their last menses (menopause) with the stage including up to 12 months of amenorrhea. During this stage, women become symptomatic (i.e hot flushes, depressive symptoms, sleep problems, decreased libido) and therefore their quality of life becomes compromised. Many tools have been designed to evaluate these symptoms. Health care provider need to have a correct understanding of these physiological changes related to ovarian functional decline. In turn, this will help guide physicians to appropriately management and treat women during this stage.

(SCHOLARSHIP05) Scholarship-course 5

The post-menopausal hormone therapy

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University of Malta. Dept of O&G

There is no single post-menopausal hormone therapy. This is an important concept that needs to be appreciated. The second important concept is that this form of therapy is in fact replacement therapy and needs to be considered in the same way as one would consider thyroxine replacement in someone who is hypothyroid.

Essentially post-menopausal hormone replacement therapy falls into two major pharmaceutical components. Oestrogen replacement, and oestrogen/progestogen replacement.

Oestrogen tends to be the natural 17β Oestradiol. The emphasis is on natural since claims of other natural or phyto oestrogens as being natural are spurious and subject to qualification. 17β-Oestradiol, E_2 is the major natural oestrogen produced in reproductive life.

Particularly to women with a uterus, oestrogen is followed by progesterone (Progestogen therapy), in order to prevent, endometrial hyperplasia, and eventual endometrial cancer from occurring in the uterus.

The progestogen family have different properties on the metabolic systems, cardiovascular risk, thrombosis risk and breast cancer incidence and differences between them need to be kept in mind.

Postmenopausal HRT need to be tailored to individuals.

The emphasis as per IMS, and EMAS and NAMS is on the window of opportunity for treatment and individualisation. Individualisation matters when one is considering to treat the short term effects of the menopause such as hot flushes, sweats, anxiety. Irritability or insomnia on the long term symptoms of the menopause namely osteoporosis, cardiovascular risk, connective tissue risk.

The long ongoing debate of HRT risk and breast cancer needs to be put in proper perspective with clear definition as to what type of HRT is one talking about when attributing risk. What sort of patient is being referred to, whether that patient is high risk or not and if high risk, whether a more suitable form of HRT or alternative to relieve symptoms is to be utilised.

Finally is it possible to tailor HRT so as not only to be able to avoid risk of breast cancer, but actually to be able to reduce the incidence? This seems increasingly possible particularly in the ER positive breast cancers.

(SCHOLARSHIP05) Scholarship-course 5

Decision taking in the process of treating female infertility

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It is essential that fertility treatment is individualized based on a thorough diagnostic work-up, with treatment tailored to the patients' requirements. This individualization should be kept in mind during the main decision points that occur before and during treatment. Treatment customization must include consideration of both the woman and her partner involved in the process together, including their collective treatment goals. Once treatment goals have been agreed and diagnostic evaluations performed, personalization based on patient characteristics, together with an understanding of treatment goals and patient preferences, enables the selection of appropriate treatments, protocols, products and their dosing. Following treatment initiation, monitoring and adaptation of product and dose can then ensure optimal outcomes. Currently, it is not possible to base treatment decisions on every characteristic of the patient and personalization is based on biomarkers that have been identified as the most relevant. However, in the future, the use of artificial intelligence coupled with continuous monitoring should enable greater individualization and improve outcomes. This review considers the current state-of-the-art related to decision points during individualized treatment of female infertility, before looking at future developments that might further assist in making individualized treatment decisions, including the use of computer-assisted decision making.
1 Gynecol Endocrinol. 2019 Dec;35(12):1027-1036

Scientific Societies Symposia

Adenomyosis and Endometriosis: an update (organized by the Société Européenne de Langue Française et Allemande de Gynécologie et Obstétrique - SELFAGO/EGGG)

Diagnostic accuracy of ultrasound in pelvic and deep infiltrating endometriosis

Marcel Bäumler (FR), René Druckmann (FR)
[Bäumler] CHU de NÎmes, [Druckmann] Societe Europeenne de Langues Francaise et Allemande de Gynécologie et Obstétrique

Objective:
Evaluation of the diagnostic accuracy of transvaginal ultrasound in the pre-therapeutic evaluation of pelvic and deep infiltrating endometriosis.

Methods:
Review of the current literature. Articles analyzing the correlation of ultrasound signs with clinical and surgical results are reviewed.

Results:
Transvaginal ultrasound has sufficient sensitivity and specificity to diagnose pelvic and deep infiltrating endometriosis to program appropriate medical or surgical treatment. The diagnostic accuracy can not replace that of the surgery.
In order to improve the experience of the sonographer, further investigations should show the correlation with the surgical diagnosis, but also with the clinical results of a long-term medical follow-up.

Body composition and health at menopause transition (organized by Indian Menopause Society)

Syndromic approach to bone, muscle, and fat health

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Fortis Escorts Hospital

Recently coined term "Osteo-sarcopenic-obesity" (OSO) is a syndromic approach and a new face of an old problem of obesity, sarcopenia and osteoporosis. It is an emerging problem with an increased risk of development of life-style related diseases (cancers, DM, and other diseases that cause endocrine imbalance), reduced QOL, survival and have a growing impact on healthy life expectancy with rising health care costs in developed/developing nations.

OSO is chronically deteriorating condition and is a complex of two independent but inter-related conditions that are Sarcosteopenia and sarcobesity i.e. loss of muscle mass (sarcopenia) and increased/ectopic fat deposition with bone loss with systemic metabolic dysregulation.

Critical health issue is how to lose fat mass while preserving muscle mass and bone mass? It is essential to assess for sarcopenia and osteoporosis in obese middle /older people and document obesity, low bone/muscle mass by DXA and low muscle function/ strength. After excluding secondary causes, one should initiate evidence-based interventions and refer high-risk patients to specialized clinics, where available. Regular follow-up and education of patients are paramount for successful management.

Menopause is an ideal opportunity to discuss a woman's risk profile, ensure risk perception, screen for OSO and to develop long term preventative plan. It is vital to increase not only scientific but also public awareness for the identification, prognostic significance, public health costs and ultimately the development of behavioral, nutritional, and possibly pharmacological interventions to prevent or reverse this condition. Promotion of the global initiatives at national, individual, interpersonal, organizational and community level with multidisciplinary and multifaceted approach should be advocated. Future researches with longitudinal studies on personalized whole-body approaches such as precision medicine, functional medicine and nutrigenomics are warranted.

Learning Objectives:

1. To understand the recent concept of syndromic approach (OSO), pathophysiology of individual components and outline the Diagnostic Criteria's.
2. To address prevalence of this metabolic Conundrum, its impact on overall health at midlife and beyond (Individual and society).
3. To discuss the preventive / treatment strategies: Evidence based recommendations on exercise-nutrient interventions and Pharmacological approach.
4. To identify areas for future research.

Body composition and health at menopause transition (organized by Indian Menopause Society)

DXA beyond bone health

Meeta Meeta (IN)
Tanvir Hospital

The knowledge of body composition is important as it plays a vital role in health and disease. The appearance, performance, quality of life and longevity depends on the body composition. The changes in body composition with ageing results in diseases like osteoporosis, sarcopenia, shift in adipose tissue leading to metabolic syndrome, sarcopaenic and osteoporotic obesity. These disease have along window period before they present. The moot question is are these disorders preventable, treatable and can they be diagnosed early? Precise and accurate measurements of body composition useful in achieving a greater understanding of human energy metabolism in physiology in different clinical conditions and in evaluating interventions

Dual-energy X-ray absorptiometry (DXA) is the gold standard for diagnosis and monitoring of osteoporosis. DXA is the reference method for measuring bone mineral density at the lumbar spine and proximal femur DXA is useful in evaluating muscle and fat health. In the acquisition time of DXA (5 to 10 minutes) the rapid assessment of whole body composition or of a region of the body based on whole-body imaging can be done. The measurement of body composition by DXA is noninvasive, low cost and very low irradiation (2.6 to 75 mSV) compared to other techniques including computed tomography and magnetic resonance imaging.

The expanded indications for DXA are measuring overall and segmental adiposity, muscle mass and Resting Energy Expenditure. Visceral fat is an independent predictor foe all cause mortality, for independent of age, race, and sex. The DXA preciously differentiates between the fat mass, lean mass and bone mass in different segments of the body. It is superior to the measurement of body mass indexing defining obesity because it preciously measures fat and is not gender specific. It is indicated in cases of obesity,, cardiovascular risk, cystic fibrosis, HIV diet and exercise effectiveness physical training/exercise, injury rehabilitation, diet and exercise effectiveness, GH deficiency, hyperparathyroidism, PCOS, hypogonadism.

Sarcopenia, an age-related muscle mass decline for which skeletal muscle index is usually used for muscle mass computed as the ratio of appendicular skeletal muscle mass over height squared by the DXA. Fat and muscle have different energy needs, it takes more energy to maintain muscle than fat The Resting Energy Expenditure goes up with increases in muscle mass even if the weight doesn’t change.

Contraception in special situations (Symposium organized by SOCHEG - Sociedad Chilena de Endocrinología Ginecológica)

Contraception and depression

Patricio Barriga (CL)
Universidad Finis Terrae

Endogenous and exogenous sex steroids can produce different changes in mood modulation. The normal neuroendocrine changes that occur during the woman's menstrual cycle modulate the production of different neurotransmitters and receptors involved in the response, the best known being GABA.

Abnormal or pathological manifestations produced by normal hormonal changes (sex steroids, mainly ovarian) and their interaction in the CNS, would be responsible for some pathological psychiatric disorders, such as premenstrual dysphoric disorder (DPMS), postpartum depression or mood disorders that accompany women during its pre and postmenopausal climacteric, to mention the most known.

We know that the use of exogenous hormonal therapies such as hormonal contraception (HC) or menopausal hormone therapy (MHT), are part of the direct or complementary therapeutic arsenal to improve these conditions.

There is no substantiated evidence to show that hormonal contraceptives are the cause of depression or suicide (be it ideation, attempt or consummation). While sexual steroids would have an impact on women's mood and mood, these effects are not fully known. Also, recent epidemiological studies have also not shown the increase in depression, especially in adolescent women, as if they have observed other studies.

The risk and bias of some studies based solely on data logging do not consider that many of these women are likely to receive other drugs that can induce pharmacological interactions and, worse, do not consider individual aspects of sexuality.

HC is used to manage different gynecological medical conditions of women (hirsutism, abnormal uterine bleeding or severe dysmenorrhea), without any change being found, in the manifestations of depressive symptoms when compared with placebo.

The evidence shows that the use of HC is safe and that the potential serious risks are very scarce, independent of the formulation or route of use. You should always consult a health professional for adequate contraceptive counseling, including hormonal and keep a regular check of its use.

It is recommended in the starter, control at least within of the first 3 months of using an HC, period in which mood alterations may appear.

In conclusion, the use of HC can reduce depressive symptoms, they are not a cause of depression or suicide, including not reporting a suicide attempt or ideation.

Contraception in special situations (Symposium organized by SOCHEG - Sociedad Chilena de Endocrinología Ginecológica)

Contraception in drug addict women

Paula Vanhauwaert (CL)
SOCHEG

Drug addict women are at increased risk of unintended pregnancy, not only once, but repeatedly. We also know this are high risk pregnancies for both the mother and the baby. Besides many of this children are neglected.
Sanitary personal have many prejudices about this population and their contraceptive opinions and choices. This conference intend to change this prejudices and improve the contraceptive care of this population.Drug addict women are at increased risk of unintended pregnancy, not only once, but repeatedly. We also know this are high risk pregnancies for both the mother and the baby. Besides many of this children are neglected.
Sanitary personal have many prejudices about this population and their contraceptive opinions and choices. This conference intend to change this prejudices and improve the contraceptive care of this population.

Different faces of hyperandrogenemia (organized by the Latvian Society of Gynecological Endocrinology)

Hyperandrogenic effects on female fertility and pregnancy outcome

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iVF Riga Infertility Clinic

Hyperandrogenism or androgen excess is a common endocrine disorder of women of reproductive-age, with a prevalence of 5-10%. The majority of patients with hyperandrogenism will have polycystic ovary syndrome.
Ovarian androgen synthesis and regulation are essential to ensure adequate steroidogenesis and folliculogenesis. In primates, there is evidence for a direct impact on the number of small antral follicles and on the process of chronic anovulation.
Androgens play a key role in the physiological control of ovarian function, acting both as precursors for oestrogen biosynthesis and directly via the ovarian androgen receptor.
In women facing clinical hyperandrogenism, determination of serum androgens (testosterone, androstenedione, 17-OHprogesterone, DHEA-S) is helpful in separating patients according to the presumed ovarian, adrenal or idiopathic origin of the clinical symptoms. Idiopathic hyperandrogenism in young adolescents without menstrual dysfunction and infertility has been attributed to hypersensitivity of peripheral tissues to androgens without any excess in androgen production. In this situation, the reason for consultation is mostly cosmetic and anti-androgen agents are indicated.
Chronic anovulation, Clinical and/or biochemical signs of hyperandrogenism, Oligo- and/or anovulation, Clinical and/or biochemical signs of hyperandrogenism, Polycystic ovaries, common clinical manifestations in patients with infertility.
It is very important to use existing guidelines in clinical work that will help at the stage of examination of the patients, establish a diagnosis and choose the appropriate protocol for ovarian stimulation and preparation of the endometrium. Must take into account age, BMI, the presence of metabolic syndrome, as well as problems of the cardiovascular system.
Widely used stimulation protocols for patients with hyperandrogenism and PCOS are Letrozole, Clomiphene, as well as mini stimulation with recombinant gonadotropins.
It is known that the quality of oocytes in patients with hyperandrogenism and PCOS in 30-40% of cases is not mature (qv, M1), which leads to low fertilization and a large number of aneuploid embryos.
Most patients with PCOS and hyperandrogenism have endometrial maturation defects, which lead to a reduced possibility of implantation. In patients with PCOS, in 70% of cases, non-receptive endometrium was detected, with premature maturation in most cases.
The correct assessment of patients before the IVF treatment, as well as the preliminary preparation and normalization of hormonal levels and metabolism, positively affect the amount of mature oocytes, therefore the amount of euploid embryos and the maturity of the endometrium, significantly increase the chance of pregnancy in IVF cycles.

Different faces of hyperandrogenemia (organized by the Latvian Society of Gynecological Endocrinology)

Different clinical presentations in complete androgen insensitivity syndrome

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Riga Stradins University

Context

Complete androgen insensitivity syndrome (CAIS) is a congenital disorder of sex development that is characterized by a female phenotype and a 46, XY karyotype due to allelic variants in the androgen receptor (AR) gene, which is located in the X-chromosome. These changes lead to complete resistance to the biological actions of androgens and foetal sex differentiation into a female phenotype. In adolescence, CAIS is characterized by excess aromatization of androgens to oestrogens and the absence of opposing androgen action due to androgen receptor dysfunction with consequent development of secondary female characteristics.

Objective

For a long time, generally accepted recommendations suggested performing gonadectomy after puberty due to the risk of malignancy. However, recent studies have revealed a slightly lower risk of developing testicular germ cell tumours of approximately 5% in androgen insensitivity syndrome, and although germ cell neoplasia in situ is found in 14% of patients, malignant progression appears to be a rare. Therefore, the practice of routine prophylactic gonadectomy in adults with CAIS appears questionable and the recommendations – less stringent.

Patient

A 48-year-old patient was admitted to the hospital with a suspected testicular germ cell tumour due to CAIS. The patient's main complaints included progressive and transitory edema, general malaise and a mobile formation in the left groin gradually grown to 2.5 cm over the previous 4-5 months. CAIS had been detected in 1986, when the patient was examined due to primary amenorrhea, and her karyotype was analysed and confirmed 46,XY. At the time of admission to the hospital, a biochemical evaluation revealed excessive expected luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and androstenedione levels. Investigations including a pelvic ultrasound and magnetic resonance imaging (MRI) examination revealed oval structures in both inguinal canals and identified a residual testicular structure measuring 9.5 cm^3 in the right hypogastrium.

Results

The patient underwent a two-stage surgical intervention with the first stage of bilateral orchidectomy performed through an inguinal approach. During the second stage of the surgical procedure, a laparoscopic orchidectomy was performed. To confirm the diagnosis genetically, PCR and bidirectional Sanger sequencing for the coding regions and exon/intron boundaries of the AR gene were performed. Previously unreported genetic variation with amino acid changes in the ligand binding domain of the 6th exon of the AR gene, where phenylalanine at the 805th position was exchanged for cysteine was found.

Different faces of hyperandrogenemia (organized by the Latvian Society of Gynecological Endocrinology)

Challenges with NC-CAH in patient-oriented approach

Ineta Vasaraudze (LV)
I. Vasaraudze´s Private Clinic

NC-CAH is a comparatively common disorder regardless of ethnicity; however most cases go undiagnosed, especially in males.
Allele frequencies have been investigated in many different populations and, contrary to what had been thought before, heterozygosity for non-classic mutations was relatively common regardless of ethnicity.
Early morning baseline values of 17 OHP (the biochemical hallmark of 21-hydroxylase deficiency and the main substrate for the 21-hydroxylase enzyme) as a good initial screening test and further evaluation with ACTH stimulation and, in the case of borderline results. genetic testing, is recommended.
Genetic testing is an alternative diagnostic tool for NC-CAH and it can be used when biochemical results are uncertain or when genetic counseling is necessary prior to conception. CYP21A2 genotyping should be performed to identify heterozygote carriers.
Most patients have been identified during investigations for symptoms for which they have sought medical attention, the majority of individuals diagnosed with NC-CAH will receive some kind of treatment, at least for a certain period of time.
At least annual physical examination and hormone measurements (morning 17OHP and androstenedione) are recommended by the Endocrine Society, but no guidance is privided about specific targets.
The treatment decision should be based on assessment of the facts and should follow an individualized approach.
Genetic counseling is strongly advised in NC-CAH women who wish to conceive, as well as genotyping of the father.
The overall management of the patient also includes management of the probable complications of glucocorticoid therapy or metabolism-related manifestations of the disease.
Nevertheless, studies on the fertility outcome have shown that 53–68% of the women with NC-CAH conceived spontaneously before diagnosis and treatment. After the start of hydrocortisone treatment, most women (78%) became pregnant without ovulation stimulation. Patients who became pregnant spontaneously had, overall, fewer clinical symptoms of androgen excess, although there was no difference in the frequency of mild and severe mutations between the groups. Glucocorticoid treatment shortened the time to conception from about 1 year to less than 6 months.
Studies focusing on the specific difficulties that patients with NC-CAH face, both those with a late clinical diagnosis and those with a neonatal diagnosis obtained by screening, are warranted.

Endocrinology of gender - latest news (organized by SSEG - Serbian Society of the Endocrinology of Gender)

Melatonin- novel approaches in improbving reproduction and general health

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Melatonin, a somewhat mysterious substance, might be a crucial factor in regulating numerous processes in human reproduction. It is a powerful antioxidant which has an essential role in controlling several physiological reactions, as well as biological rhythms throughout human reproductive life. Melatonin, which is referred to as a hormone, but also as an autocoid, a chronobiotic, a hypnotic, an immunomodulator and a biological modifier, plays a crucial part in establishing homeostatic, neurohumoral balance and circadian rhythm in the body through synergic actions with other hormones and neuropeptides.
Melatonin is implicated in the control of pubertal onset, sexual maturation, timing of ovulation, reproductive life potential, pregnancy protection, as well as in alleviation of menopause-related symptoms and disorders. With its immunological and oncostatic properties, melatonin is one of the best ‘‘intracellular defenders’’ with a potential to act on many target tissues and organs, being beneficial not only for preserving reproductive health but also in general health. As multifunctional antioxidant, it delays ovarian aging via multiple pathways. This therapy may be used for enhancing ovarian function and managing various ovarian diseases including premature ovarian insufficiency, for fertility recovery and pregnancy protection, as well as for the prevention and treatment of serious neurodegenerative and malignant disorders. Investigation of its use is essential not only for reproductive well-being, but also for improving general health and life in humans.

Endocrinology of gender - latest news (organized by SSEG - Serbian Society of the Endocrinology of Gender)

Polycystic ovary syndrome and reproduction

Svetlana Spremovic Radjenovic (RS)
Clinical Centre of Serbia

Polycystic ovary syndrome (PCOS) is not necessarily and always associated with anovulation or oligo ovulation, but often it is. From the therapeutic point of view, it is not the same if the patient has the metabolic problem or not, because if the insulin resistance is diagnosed and no other infertility problems are present, insulin sensitizing drugs are a good way for young women to restore regular ovulations and as a consequence, to become pregnant. Our randomized study revealed the similar influence of myoinositol and metformine on insulin concentration in lean PCOS women, but the better effects of myoinositol on pregnancy achievement. For the obese anovulatory PCOS women the metformin or myo/chiroinositol combination is the better choice. Prospective randomized study point to the Influence of myoinositol in PCOS women undergoing IVF in the Improvement of oocyte quality, fertilization rate, and embryo quality. There is the growing evidence about effectiveness of aromatase inhibitors for ovulation induction in PCOS women; the advantages of aromatase inhibitors are single follicle ovulation and good endometrial response. The live birth rate in our cohort of 150 women are 15% in the first attempt of ovulation induction. In comparison of 9% live birth rate after Clomifen citrate induction, that is significantly better result. The safety concerns of aromatase inhibitors are resolved after numerous randomized studies in Canada and USA, summarized in two metaanalyses. All freeze technology combined with modified triggering of ovulation in short antagonistic protocols, offers the better results for controlled ovarian stimulation in IVF cycles of PCOS women, and great relief in relation to ovary hyperstimulaton syndrome (OHSS) risks. And last, but not least, the pregnancies of PCOS women are high risk pregnancies and require tests for gestational diabetes in second half of pregnancy, especially if hyperinsulinemia was diagnosed before pregnancy, and require detection of hypertension in pregnancy and preeclampsia, especially if women are obese. Metformin and myoinositol use in pregnancy, indications and risks, are contradictory issue at the moment.

Endocrinology of gender - latest news (organized by SSEG - Serbian Society of the Endocrinology of Gender)

Transgender heart

Svetlana Vujovic (RS)
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Transsexualism represents incongruence between chromosomal, phenotype, gonadal and psychic sex. Every cell has a sex. Hypoestrogenism in women in the menopause and low levels of testosterone in men induce cardiovascular diseases through many mechanisms. Estradiol and progesterone receptors are present on the endothelial cells, fibroblasts, cardiomyocytes of the heart. The greatest density of androgen receptors in male is in the heart. Gonadal steroids influence lipid metabolism, insulin sensitivity and blood pressure in both sexes. Common drugs effects, treating cardiovascular diseases, depend on gender specific polymorphic variants in genes including MDR1, APOZ, ACE, preproendothelin-1, microsomal triglyceride transfer protein.

Gender affirming therapy can influence heart function. Electrophysiological differences and conduction system characteristics are gender dependent. Therapy with Testosterone in male transsexuals regulates cardiac action, potential, calcium homeostasis and has effects on endothelial cells in typical women's heart before initiating therapy. It increases repolarizing potassium + current density and protect against arrhythmia in women. Estroprogestagen therapy in female transsexuals can decreases left ventricle scarring after myocardial infarction and increase it's function. Myocardial response to acute ischaemia is gender dependent (apoptotic rate, Bax expression, cardiac function, myocardial healing, remodelling). Acute application of testosterone increases intracellular calcium in cardiac myocytes eliciting voltage by IP3 receptors. Phosphalamban, regulator of cardiac contraction, expression is increased in males. Androgen receptor overexpression in myocytes increases mitochondrial enzymes activity and oxygen consumption, induces vasodilatation and increases blood flow.

Gender differences, including differences in heart size volume, pumping activity in combination with endocrine and metabolic changes, as well as life style, may play key factor for the aging process. Does the heart characteristics, female or male, depend on receptor density, or gonadal steroid amonuts or philosophy of life on this Planet continuously changing polarities?

Optimising health, happiness and wellbeing after menopause (organized by IMS - International Menopause Society)

Optimising health after menopause

Sunila Khandelwal (IN)
Fortis Escorts Hospital

The magnitude of problem of menopause is growing as a significant public health issue globally with increasing average life expectancy. It is important for women to be aware about both mental and physical changes that occur after menopause and the support they have, to make the midlife crisis an opportunity instead of a challenge. Early age at menopause in developing countries with sizable increase in number of women with premature and induced menopause, has further several implications as it predisposes to chronic health disorders (osteoporosis, heart disease, DM, cancers and dementia) a decade earlier. Clinicians should provide easier, effective safe solutions as per their need for converting miserable life into meaningful life.
Goal is to offer graceful aging by "one stop shop" services from specialty menopause clinic for individualized management based on risk score assessment using and available diagnostic tools during well women screening. They can start re-framing menopause as a period of new beginnings, rather than endings.
To improve health related quality of life in later years, women need attention, assurance and assistance. They can make informed healthcare decisions with menopause practitioners by knowing-
• Physical symptoms throughout all phases of menopause
• Early detection of heart disease, breast cancer and other health risks
• Osteoporosis prevention – how to maintain strong, healthy bones
• Treatments (hormonal and/or non-hormonal), including MHT
• Therapeutic lifestyle management and complimentary alternative approaches.
• Staying sexually active during menopause
This presentation will highlight the importance of early intervention (Whom, when and How?) for empowering women in their second adulthood. HCP's need to be proactive towards implementation of preventive health care strategies with counselling, interventions and manage them comprehensively with individualized multidisciplinary approach based on their culture and holistic views, without or with use of MHT. Application of nutrigenomics towards personalized dietary recommendation is step forward in this direction. Preventive medicine for women health is a new concept; an academic field which should be assigned and promoted by obstetrician and gynecologist with active involvement in the care of women in this aging society. The mission of IMS is to help women to make smarter moves with safer choice for second adulthood. Research continues and information keeps changing.

Optimising health, happiness and wellbeing after menopause (organized by IMS - International Menopause Society)

Identifying depression and maintaining happiness

Pauline Maki (US)
University of Illinois at Chicago

Optimizing wellbeing during the menopausal transitions involves maximizing positive mood/happiness and minimizing negative mood/depressive symptoms. For happiness, longitudinal data indicate that positive mood is stable across the menopausal transition, though the factors that relate to positive mood change over time. Specifically, early in the menopausal transition, interpersonal stress and negative attitudes toward aging negatively influenced positive mood. Later in the transition, positive mood was associated with living with a partner, increased work satisfaction, absence of dysphoric symptoms, low interpersonal stress, few major life events and few daily hassles. In this way, both intrinsic and extrinsic factors play a role in women's positive mood across the menopausal transition. Regarding negative mood, prospective cohort studies reliably increases in depressive symptoms as women transition through the menopause. The risk of major depressive disorder (MDD) also increases as women transition through the menopause, though this risk is primarily observed in women with a history of MDD. Recent evidence-based guidelines from the North American Menopause Society and the National Network on Depression Centers recommend that antidepressants and psychotherapies remain as front-line treatments for MDD during the menopause transition. Treatment of vasomotor symptoms (VMS) in women with MDD is key, as these symptoms can exacerbate mood problems. VMS increased risk for elevated depressive symptoms but not clinical depression. Estrogen therapy (ET) may have direct benefits in preventing and treating depression in the perimenopause. A longitudinal investigation of women over two decades across the menopausal transition and beyond showed that negative mood and depressive symptoms decrease with age, a finding consistent with the broader literature.

Ovarian dysfunction in reproductive years (organized by SOBRAGE -Sociedade Brasileira de Ginecologia Endócrina)

The ovarian and uterine transplantation. Brazilian experience

José Maria Soares-jr (BR)
Faculdade de Medicina da Universidade de São Paulo

The experience of the Discipline of Gynecology, Department of Obstetrics and Gynecology, USP School of Medicine on Ovarian and Uterine Transplantation will be presented. First part (A) is our experience of cryopreservation of ovarian tissue (including the use of melatonin). After that I will present our experience on human uterine transplantation (B).

a) Improving the techniques for ameliorating the cryopreservated ovaries is a great challenge. This study aims to evaluate the effects of melatonin added to cryoprotector on the rat ovarian graft quality. Twenty female rats were allocated to two study groups of ten animals each: 1) control group: ovaries cryopreserved in standard protocol; and 2) melatonin group: ovaries cryopreserved in medium with melatonin. Following a 24-hour freezing, the whole ovaries underwent an autologous and avascular transplant with retroperitoneal placement. After postoperative (PO) day 15, daily vaginal smears were collected for estrous cycle characterization. Between PO day 30 and 35, the animals were euthanized and ovarian grafts collected for histological and immunohistochemical (Ki-67, cleaved caspase 3, TUNEL, von Willebrand factor, estrogen and progesterone receptors) analysis. The three remaining rats from each group had their ovaries studied immediately after thawing so as to determine the cryopreservation effects.

Results

The use of melatonin promoted faster restart of estrous cycle an increase in: mature follicles, collagen type I, von Willebrand factor, Ki-67 and estrogen receptors in ovaries. There was reduction in apoptosis by TUNEL on follicles and corpora lutea and collagen type III. Melatonin may promote better quality of ovarian grafts.

b) A 32-year-old woman with congenital uterine absence (Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome) underwent uterine transplantation in Hospital das Clínicas, University of São Paulo, Brazil, from a donor who died of subarachnoid haemorrhage. The recipient had one in-vitro fertilisation cycle 4 months before transplant, which yielded eight cryopreserved blastocysts. Pregnancy occurred after the first single embryo transfer 7 months post-transplantation. No blood flow velocity waveform abnormalities were detected by Doppler ultrasound of uterine arteries, fetal umbilical, or middle cerebral arteries, nor any fetal growth impairments during pregnancy. No rejection episodes occurred after transplantation or during gestation. Caesarean delivery occurred near gestational week 36. The female baby weighed 2550 g at birth, appropriate for gestational age, and along with the mother remains healthy and developing normally 7 months post partum. This was the first case worldwide of livebirth following uterine transplantation from a deceased donor in a patient with MRKH syndrome.

Practical Gynecological Endocrinology (organized by PSGE -Polish Society of Gynecological Endocrinology)

Estrogens and their modulation of pain processing

Monika Grymowicz (PL)
Medical University of Warsaw

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain transmission is essential to maintain the integrity of the body. Women have higher than men prevalence of conditions associated with chronic pain such as irritable bowel syndrome, interstitial cystitis, temporomandibular joint disorder, chronic fatigue syndrome or fibromialgia. Moreover, women show greater sensitivity to nociceptive stimuli (thermal, electrical or pressure). However, pain severity varies across the menstrual cycle and pregnancy induces antinociception in animal and human studies.

Numerous animal and human studies on the role of estrogens and nociception showed very variable findings. Definite conclusions whether estrogens have pronociceptive or antinociceptive effect are difficult to draw from the animal model studies because of wide variety of types of stimulation and behavioural tests employed, use of different species and strains and different periods from ovariectomy. Studies in humans are even more complicated due to huge influence of social and emotional factors.

Estrogens, apart from their role in reproduction, regulate somatosensory systems having a profound effect on morphological structure of nervous system as well as on temporary physiological events. Estrogen's receptors (ER) are widely distributed in the nervous system. ERα predominate in the ventromedial hypothalamus and in the spinal and trigeminal dorsal horns, whereas ERβ are found mainly in the cortex and the cerebellum, preopic area and the thalamus. Estrogens exhibit their organisational effect by influencing neuronal migration, response to ischaemic damage, size of the receptive fields of sensory nerves and blood perfusion in the brain. Activational effect of estrogens is related to the regulatory influence on most neurotransmitter systems. The antinociceptive effect of estrogens seems to be achieved by strong modulation of the endogenous opioid system.

Although the interaction between estrogens and pain transmission is unambiguous, the exact mechanisms cannot be easily explained or narrowed down to one specific action. Future studies on gonadal hormones and pain will certainly better explain mechanisms and thus, increase the possibility of better treatment.

Practical Gynecological Endocrinology (organized by PSGE -Polish Society of Gynecological Endocrinology)

How to diagnose and treat hormone-producing ovarian tumors?

Agnieszka Podfigurna (PL)
Poznan University of Medical Science Poznan, Poland
Polish Society of Gynecological Endocrinology

Hormone-producing ovarian tumors include tumors that are capable of synthesizing mainly steroid hormones - estrogens and progesterone, but also other hormones that are not directly related to ovarian tissue. These include carcinoid, ovarian thyroid tissue (struma ovary), or β-HCG-producing germ cell tumors. Hormone-producing ovarian tumors can belong to any group of ovarian tumors, but most often gonadal tumors that originate from gonadal tissues, both female and male, have such ability. Their incidence is estimated at 3-8% of all ovarian tumors. Tumors that produce female sex hormones cause estrogen overproduction and, among other things, lead to pathological endometrial hyperplasia and even cancer. In turn, androgen secreting tumors cause virilization symptoms.
Suspicion of the presence of a virilizing tumor should be the basis for computed tomogra-phy (adrenal assessment), transvaginal ultrasound examination (ovarian assessment). If hormonal tests suggest the presence of a virilizing ovarian tumor, no tumor of the adrenal gland was found in computed tomography, despite the normal result of ovarian ultrasound examination, due to the fact that virilizing tumors may be very small, laparoscopy should be offered to the patient. In case of coexistence any other pathology of the reproductive organ - laparotomy should be considered.

Progestogens in Gynecology and Obstetrics: an up-date. (Symposium organized the European Progestogen Club)

Progestogenes and menopause

Alfred Mueck (DE)
University Women's Hospital of Tuebingen

With each type of HRT similar good efficacy regarding climacteric symptoms or prevention in bone and cardiovascular system can be achieved. However, there are differences in terms of possible risks which can be reduced by the choice of type, dosage and application form of HRT. This should be decided on the basis of the whole evidence, i.e. not only derived from Women's Health Initiative (WHI) study where only one type of HRT has been tested. We prefer to treat with the natural estrogen, i.e. estradiol, instead of equine estrogens which are a mixture of estrogens not natural for humans. Likewise it seems to be reasonable, also to use the natural progestogen, i.e. progesterone. However, synthetic progestogens are superior to progesterone with respect to endometrial action, and the first rule for the choice of a progestogen is to get endometrial protection from developing endometrial cancer. Furthermore, bleeding problems mostly are the first complaints in perimenopause, and often the reason for patients and doctors to HRT. However, it has been demonstrated that using progesterone also endometrial protection can be achieved, not only in sequential design (like in the PEPI study, 1996), but also in continuous combined design, as just recently has been published (REPLENISH study, 2019). Nevertheless, using progesterone, it is advisable to check regularly endometrium and bleeding patterns, to use not too low dosages (200-300 mg sequentially, 100-200 mg continuously) and to prefer vaginal application if the patient is compliant. Treating in the first official menopause clinic in China about 500 outpatients every day, we have good experience using dydrogesterone, which has similar positive properties like progesterone, but stronger endometrial efficacy. Using progesterone or dydrogesterone, compared with synthetic progestogens like MPA or NET, NETA, there are less side effects in the metabolic and vascular system (no vasoconstriction) with reduced risk of stroke and venous thromboembolism, and perhaps also less breast cancer risk, as can be suggested from experimental studies and observational trials. Beneficial cardiovascular effects of estrogens are not antagonized, with advantages e.g for patients with (risk of) diabetes or metabolic syndrome. Thus our choice of HRT mostly is estradiol, often as transdermal application, combined with progesterone orally or preferably vaginally, and in patients with bleeding patterns combined with dydrogesterone.

Progestogens in Gynecology and Obstetrics: an up-date. (Symposium organized the European Progestogen Club)

What is the optimal luteal support in ART

Sven Skouby (DK)
Clinical Medicine, University of Copenhagen

Although the need of luteal phase support (LPS) in IVF/ICSI cycles is well-known the optimal start, dosage, route and the duration of the luteal phase support is still subject of debate. Start of luteal support has not been studied properly Data suggest that the optimal period to start with the luteal phase support would be in the window between the evening of the day of oocyte retrieval and day 3 post oocyte retrieval and should continue at least until the day of the pregnancy test. However, the majority of IVF-centers worldwide provide progesterone support up to 8 weeks of pregnancy. Among the well-established routes of luteal support, oral dydrogesterone and subcutaneous progesterone represent new and interesting routes of progesterone administration. The current studies support these routes of progesterone administration use in terms of comparable pregnancy rates and pregnancy loss rates to vaginal and intramuscular progesterone. Furthermore, the acceptance and tolerability among patients seems to be even better. In the frozen-thawed embryo transfer, dydrogesterone and vaginal progesterone are not effective as monotherapy treatments; however, when combined there is no reason to avoid one or the other in this setting. The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg once daily for intramuscular progesterone, 25 mg once daily for subcutaneous progesterone 90 mg once daily for vaginal progesterone gel, 200 mg three times daily for micronized vaginal progesterone in-oil capsules 100 mg two or three times daily for micronized vaginal progesterone in starch suppositories 400 mg two times daily for vaginal pessary. Daily dosages of 30 mg dydrogesterone are most frequently used for LPS. Long-term offspring health studies are currently lacking. Evidence from 2 RCTs shows no difference in the rate of congenital anomalies as compared to natural progesterone

Regulation of implantation (organized by DGGEF - German Society for Endocrinology and Fertility)

Embryo quality and implantation

Ariane Germeyer (DE)
University hospital Heidelberg

While the techniques of ART have evolved over the last 40 years adding new fertilization techniques, like intracyctoplasmatic sperm injection (ICSI) and testicular sperm extraction (TESE) the relevance of the embryo quality for implantation remains high. Goal of all practioners is to improve the ART success by selection the most viable embryo. Despite morphological criteria, that are used according to the Gardner score, the implementation of time lapse imaging has added morphocinetic factors. Furthermore, in recent years additional automated time lapse selection systems, like EevaTM have been developed. Last but not least, long-term cultures, so called blastocyst cultures, are commonly used nowadays, in order to increase the success rate of ART. Nevertheless, the maternal age remains an important factor. But how do these really affect the outcome? And does a low ovarian reserve potentially influence ART success? Does genetic testing of the embryo improve live birth rates? And is there a difference between chromosomal integrity of embryos from natural cycle IVF vs. ovarian hyperstimulation? These factors are looked at and discussed using current literature.

Role of epigenetic and endocrine origins in obesity, metabolic syndrome and breast cancer in women (organized by USGE Ukrainian Society of Gynecologists Endocrinologists)

Metabolic syndrome and women's reproductive health

Natalia Pedachenko (UA)
NMAPE Shupik by name

Objective

Maintaining reproductive health in women with metabolic syndrome (MS) through establishing relationships between reproductive health disorders, endometrium and breast diseases and adipokines levels.
Patient(s) 68 women with metabolic syndrome and 54 healthy control patients.

Methods

The diagnosis of MS was established according to the criteria of the International Diabetes Federation (2006). PCOS was diagnosed by us according to the Rotterdam ESHRE / ASRM Consensus Workshop Group, 2003.
We performed an ultrasound (ultrasound) examination of the pelvic organs with the use of transvaginal transducer. The size and presence of structural changes of the uterus, the state of the endometrium, its thickness, the presence of inclusions to determine the indications for a possible biopsy. Breast examination was performed according to the algorithm proposed by the American Cancer Society (1996). The anatomical and functional state of adipose tissue was determined by ultrasound, computer tomography and serum adipocytokine content.
The obtained digital data were processed using licensed statistical programs Excel Microsoft Office 2003 and Stata 12 using methods of variational statistics.

Results

It was established that in patients with MS, PCOS and infertility, as well as high level of hyperproliferative processes of endometrium and benign breast diseases are observed.
After the BMI correction, the accuracy of intra-abdominal fat measurement by ultrasound and CT scan was independent of BMI (BMI≥36.2 kg/m^2: r = 0.734, p <0.05; BMI<36.5 kg/m^2: r = 0.742, p <0.05).
We found out that an increase in insulin levels > 17.5 μIU/ml increases the risk of developing benign breast pathology in 11 times (relative risk 10.9; p <0.05), decrease in adiponectin <14.6 pg/ml - 2 times (relative risk 2.0; p<0.05), and decrease in lipocalin < 49.0 ng/ml - 3 times (relative risk 3.46; p <0.05). It was also found that the risk of developing endometrial hyperplasia increases with an increase of leptin > 1000.0 ng/ml by 8-fold (relative risk of 8.05; p <0.001), insulin > 26.0 μIU/ml 4-fold (relative risk 4.05; p <0.001) and adiponectin <12.0 pg/ml – in three times (relative risk 3.23; p <0.001).

Conclusions

There are given thresholds concentrations of adiponectin, leptin and insulin, which increase the risk of benign breast disease and endometrial hyperplasia.

Role of epigenetic and endocrine origins in obesity, metabolic syndrome and breast cancer in women (organized by USGE Ukrainian Society of Gynecologists Endocrinologists)

From nipple discharge to intraductal cancer. Reasons, diagnostics and management

Aleksey Aksenov (UA), Denys Pominchuk (UA), Ivan Smolanka (UA)
[Aksenov] [Pominchuk] Verum Expert Clinic, [Smolanka] National Cancer Institute

Objective
Discharge from the nipple of the breast is the third most common symptom in a clinical examination of the breast and can be a symptom of a benign and malignant tumor. Among benign intraductal tumor pathologies, the most common and having the highest risks of malignancy are intraductal papillomas (the risks of malignancy are from 8 to 23%) and DCIS (the risks of transition to invasive breast cancer are up to 48.5%). The aim of the study was to develop an optimal diagnostic program for patients with abnormal discharge.

Patient(s)
The study included 283 patients with abnormal discharge.

Methods
At the first stage, a cytological study of the separated ducts was performed. With a positive response, ductoscopy was performed. When tumor growth was detected, removal was performed with a histological examination. In the absence of pathology in the cytological analysis of secretions, patients studied the level of prolactin and conservative therapy was prescribed. When suppressing secretion from the nipple, the patients went into the observation phase. In the absence of an effect on the ongoing therapy, ductoscopy was performed. Of 283 women, 67 (23.67%) were diagnosed with intraductal papilloma during cytological examination with ductoscopy. Of 216 patients who did not receive the effect of the treatment, 19 patients underwent ductoscopy and 6 patients had a tumor process.

Results
In 67 patients with postoperative histology, intraductal papilloma was confirmed in 17 (25.37%) patients, 27 (40.29%) patients had a combination papilloma with sclerosing adenosis, 8 (11.9%) atypical hyperplasia, 9 (13.43%) patient DCIS with intraductal papilloma, 2 (2.98%) had a combination papilloma with fibroadenoma, 4 (5.97%) patients a combination papilloma with invasive intraductal cancer. Concomitant pathology and genetic risk factors were studied. In 28 (41.7%) patients, changes in other organs with hormonal imbalance were revealed, combined pathology was detected in 8 (11.9%) patients, 6 patients had a history of cancer in the family along the female line.

Conclusions
The optimal diagnostic combination for abnormal discharge from the nipple is a cytological examination followed by ductoscopy. The presence of abnormal discharge requires a multidisciplinary approach.

Role of epigenetic and endocrine origins in obesity, metabolic syndrome and breast cancer in women (organized by USGE Ukrainian Society of Gynecologists Endocrinologists)

Distinctions of endocrine regulation in view of post-contusion syndrome

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Shupik National Medical Academy of Postgraduate Education, Kiev

Objective
Stress-related changes in the endocrine systems are key mediators involved in the development of diseases associated with posttraumatic stress disorder (PTSD). Evidence suggests that those changes might be related to the duration of PTSD and shows that the study of hormonal dysregulation may provide an important framework for determining how to mitigate the effects of exposure to trauma and how to optimize plan management practices in the future including reproductive plans. The study aimed to investigate the differences in selected endocrine variables between women of reproductive age with PTSD (group A) and control subjects (civilians of reproductive age without traumatic experience) (group B), and whether these differences persist over time.

Methods
We assessed 31 Ukrainian anti-terrorist operation zone veterans with PTSD and 43 healthy volunteers (civilians without traumatic experience), all women of reproductive age, at two time points separated by 2/3 years (median; interquartile range: 2.4-3.3). Cortisol and prolactin levels were measured by radioimmunoassays. Thyroid junction (thyroid hormonal profile) was evaluated by the measurement of serum total triiodothyronine (TT3), free triiodothyronine (FT3), total thyroxine (TT4), free thyroxine (FT4), thyroxine-binding globulin (TBG), and thyroid-stimulating hormone (TSH).

Results
At the first assessment, average indicators estimate of differences between group A and controls (group B) were observed for most of the measured variables. Only prolactin levels remained significantly elevated in PTSD patients at the second assessment with low to moderate effect size estimates of differences between patients and controls in other variables. And women in group A had significantly higher total T3 levels than control subjects (civilians).

Conclusion
Observed endocrine changes in women of reproductive age with PTSD over time may depend on the duration of the static load posed by the disorder and its impact on the endocrine systems involved in stress response. Further comparison of Ukrainian women of reproductive age participating in hostilities in the anti-terrorist operation zone with PTSD and civilians of reproductive age without traumatic experience may be useful in evaluating the significance and implications of the unusual alterations in the thyroid system in PTSD.

Keywords: endocrine systems, PTSD, hormonal dysregulation, reproductive health.

Role of epigenetic and endocrine origins in obesity, metabolic syndrome and breast cancer in women (organized by USGE Ukrainian Society of Gynecologists Endocrinologists)

Hypothyroidism and vitamin D deficiency as a breast cancer precursors

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Danylo Halytsky Lviv National Medical University

Objective
Benign dishormonal breast diseases (BBD) are diagnosed in every fourth woman under age of 30, proliferative changes are considered as risk markers for developing brest cancer, which occurs 3-5 times more often with mastopathy. Vitamin D deficiency and hypothyroidism are considered risk factors for breast cancer (Eliassen A.H., 2016; Estébanez N., 2018).

Methods
The study involved 450 patients with dishormonal proliferative diseases of reproductive organs and 50 healthy women. BBD verification was carried out with ultrasound with interpretation according to the BI-RADS system. Levels of TSH, FSH, LH, prolactin, estradiol, progesterone, testosterone, 25(OH)D in serum were determined by ECLIA. Assessment D status conducted under recommendations of Central Europe experts.

Results
BBD was diagnosed in 65.7% of cases with combined dishormonal pathology of reproductive system. Highest incidence of BBD (46.6%) was between 36-48 years old, with 19.8% at 19-25 years and 37.4% at 26-34 years. BBD was diagnosed in 38.6% of women with endometriosis, 55.3% with adenomyosis, 30.5% with leiomyoma, 17.9% of patients with endometrial hyperplasia. Diffuse mastopathy prevailed with predominance of cystic component (40.9%), nodular form of fibrocystic mastopathy was diagnosed in 33.1%, diffuse mastopathy with a predominance of fibrous component in 16.2%. Fibroadenoma was first detected in 9.8%. BI-RADS category 1 was found in 24.2% of patients, category 2 BBD, respectively in 62.3%, category 3 in 13.5%. Dependence of development of BBD on hypothyroidism was established with strong direct correlation r= 0.82. Adequate D status in women with BBD was detected in 5.0% of cases (62.0% in healthy women), 37.7% it had severe vitamin D deficiency in absence of this in healthy women.

Conclusions
Hypothyroidism, vitamin D deficiency are syntrophic comorbid pathologies for BBD. With hypothyroidism, conversion of androstenediol to testosterone and estradiol is accelerated, metabolism of estradiol changes: instead of normal 2-hydroxylation, predominantly 16-hydroxylation occurs; hormonal disturbance cause change of receptor system and greater severity of proliferative changes. D-deficiency enhances expression of estrogen receptors, gene encoding aromatase enzyme, disrupts proliferation and apoptosis. Correction of hypothyroidism and D-deficiency should be considered as prevention and treatment of BBD and priority in primary prevention of breast cancer.

Role of epigenetic and endocrine origins in obesity, metabolic syndrome and breast cancer in women (organized by USGE Ukrainian Society of Gynecologists Endocrinologists)

Underestimated role of epigenetic and endocrine origins of metabolic syndrome and obesity in women

Tetiana Tatarchuk (UA), Tetiana Tutchenko (UA), Nataliia Kosei (UA), Svitlana Regeda (UA), Liliia Vasylchenko (UA), Olena Zanko (UA)

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New facets of the pathogenesis of metabolic syndrome (MS) emerged (genetic, epigenetic, environmental), expanding the range of its etiological factors beyond the framework of alimentary. For many years, obesity was considered an indispensable component of MS, but harmonized criteria of 2009 changed this principle and the entity "normal weight obesity" emerged. The idea that other reproductive disorders except polycystic ovaries syndrome (PCOS) can also contribute to early onset of MS is asserted in different studies.

The aim of the study was to determine frequency of MS according to the harmonized criteria of 2009 in the cohort of Ukrainian women of reproductive age and to study associations between MS and gynecological disorders.

Methods

1232 premenopausal women with gynecological disorders and 368 without were screened for components of MS. History, lifestyle and adiposity patterns (based on waste/hip ratio and bioimpedance visceral fat evaluation) were compared among women with MS and gynecological disorders (group I) and without (group II).

Results

Frequency of uncomplicated MS in group I was 13.72% which was significantly higher compared to both women without gynecological disorders (groupII - 5.16%) and corresponding population data from literature. The number of MS components grew with age. Greater prevalence of visceral adiposity despite normal BMI was found in group I while in group II gluteofemoral obesity was more prevalent. History analysis showed that in group I fetal programing factors, sleep disorders and puberty abnormalities prevailed while in group II most women had family history of obesity and specific familial eating habits. Most frequent gynecologic disorders in women with MS in total were combination of uterine myoma with benign breast disease and thyroid dysfunction, hyperprolactinemia and classic phenotypes of PCOS. Among late reproductive age women with MS endometrial hyperplasia, endometriosis and premature ovarian insufficiency were most prevalent gynecological disorders.

Conclusion

MS incidence among premenopausal women with gynecologic disorders is higher than in general population and among women without gynecological disorders. Epigenetic factors could define predisposition both to MS and gynecologic disorders. Not only PCOS but also other gynecological disorders such as hyperprolactinemia, uterine leiomyoma and endometriosis can be regarded as pathogenetic component and risk factors of MS early development.

Symposium organized by CSGE - Chinese Society of Gynecological Endocrinology

Long-term endometrial consequence of polycystic ovary syndrome in Chinese women

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The First Affiliated Hospital of Dalian Medical University

Context
Women with polycystic ovary syndrome (PCOS) may be at increased risk of endometrial cancer (EC). Supporting evidence is mostly retrospective data. Limited data exist on the association between PCOS and EC in Chinese women.

Objective
To evaluate the association between polycystic ovaries and EC in Chinese women.

Methods
Firstly, case report reviewed clinical data and long-term adverse endometrial consequence in two women with PCOS. Secondly, a case-control study: women with type 1 EC were identified through admission registration database at the First Affiliated Hospital of Dalian Medical University, China, and controls were randomly selected from the same database. Demographic data, reproductive history and clinical data were obtained from medical documents. Polycystic ovaries were investigated in ovaries sections. Telephone follow-up to obtain missing data. Odds ratios were estimated using logistic stepwise regression.

Patient(s)
139 aged ≤50 women with histologically confirmed type 1 EC (EC group) and 355 age-matched women with histologically confirmed uterine fibroids (Control group).
Intervention(s) – case-control study.

Result(s)
Women in the EC group displayed higher ratios of EC risk factors than the women in the Control group including body weight, diabetes, hypertension and infertility ($p<0.001$, 0.001, 0.05, 0.001). The women in the EC group also presented higher ratios of PCOS symptoms including oligomenorrhea and histologically confirmed polycystic ovaries ($p<0.001$, respectively). Moreover, EC group women had approximately a twofold increased risk of hypertension, a fourfold increased risk of diabetes and infertility in comparison with the control group women ($p<0.05$, 0.001, 0.001). As well as, EC group women had approximately a fourfold increased risk of oligomenorrhea and a sixteenfold increased risk of polycystic ovaries in comparison with the control group women ($p<0.001$, respectively).

Conclusions
Besides obesity, diabetes, hypertension and nulliparity, polycystic ovaries and oligomenorrhea may also be risk factors of EC. PCOS is associated with an increased risk of type 1 EC in Chinese women aged ≤50.

Symposium organized by HSGE- Hungarian Society of Gynecologic Endocrinology (dedicated to the memory of András Szilágyi)

Endocrine aspects of Turner syndrome

Tamas Deli (HU), Beáta Vida (HU), Olga Török (HU), Katalin Jenei (HU), Enikő Felszeghy (HU), Mónika Orosz (HU), Attila Jakab (HU)
University of Debrecen, Debrecen, Hungary

Context
The most common cause of genetic premature ovarian failure (POI) is Turner syndrome (TS), requiring life-long endocrinologic care.

Objective
Identifying and characterising the endocrine and non-endocrine symptoms and treatments of TS patients at our tertiari level university clinic.

Methods
We searched the outpatient and inpatient database of the Pediatric Endocrinology and Gynecologic Endocrinology Units of the University of Debrecen, Hungary, covering the period 01 January, 2009 to 01 June 2019. We gathered clinical data including symptoms, karyotypes, ant treatment. We also collected data about the concomittant diseases.

Results
We identified 74 TS patients. The average age was 21.6 years, the average BMI: 27.4±10.3 kg/m^2. Complete TS karyotype (45 X0) was found in 44 patients (59%), whereas 30 patients (41%) had varied mosaic TS karyotypes (e.g. 45X0/46 XX, 45X0/47XXX, 45X0/46XY) and special variations resulting in TS (e.g. 46 x del(Xp), 46 X i(xq)). 39 patients were diagnosed with TS in childhood, 32 in adolescence and 3 as adults. Elements of TS phenotype were more common in complete TS karyotype patients as compared to mosaic or variant TS, the most common being hypoplastic and distant nipples (31% vs. 13%), short neck and boader nose (29% vs. 20%), hypertrychosis (18% vs. 3%). Reversely, in our population, mosaic TS was more commonly associated with clitoromegaly (10% vs. 4%).
Growth hormone (GH) therapy was initiated between ages 8 to 12. GH therapy significantly increased the final hight of patients (149 cm vs. 142 cm, $p<0.01$). The majority of patients received female hormone replacement therapy (HRT), which was effective in preventing osteoporosis. Various concomittant diseases were found to be several times more common in the TS population than their prevalence in the general population, including structural cardiac anomaly (23%), urogenital malformations (38%), autoimmune thyreoiditis (50%), hypothyroidism (24%), coeliakia (20%), mental disorders (52%) and hearing or visual disorders (10%).

Conclusions
Almost half of the TS population we examined did not have classical 45 X0 karyotype, and these patients presented with less typical TS phenotypes. The majority of patients are diagnosed before adulthood, and early GH and HRT therapies improve the long-term outcome. Considering the frequency of cardiac, urogenital, thyroid, sensory and gastrointestinal diseases in them, all TS patients should be screened for this disorders.

Symposium organized by HSGE- Hungarian Society of Gynecologic Endocrinology (dedicated to the memory of András Szilágyi)

Insulin, to measure or not to measure – CONTRA

Tűű László (HU)
Endocare Institute Ltd.

Context
Insulin plays an important role in the regulation of female reproduction. It has significant effect on hormon production, has major influence on the hypothalamo – hypophyseal - ovarian axis, oocyte maturation, endometrial function and influences the implantation window.

Objectives
Because of its diversified action insulin is an often evaluated parameter, but its diagnostic reliability has been questioned again and again.
The laboratory methodology of insulin measurement is still not standardised. Deviances of more than 25% are not rare, values are highly variable. Insulin levels are very sensitive to exogen and endogen factors such as diurnal rhythm, stress, menstual cycle, food intake, physical activity, sleep or the lack of it, etc.

Results
Fasting insulin levels are well determined, but insulin levels during challenge test (OGTT) are not clearly defined, nor are test results reproductible within a short time period. Experts defined several cut-off values and indexes for characterizing insulin response, but due to diversity in patients' phenotypes the values and indexes were not applicable in everyday practice.

Conclusions
There is growing demand for defining exact parameters of insulin sensitivity, insulin secretion and insulin action, but despite the intense effort of researchers this is not reality yet.

Symposium organized by HSGE- Hungarian Society of Gynecologic Endocrinology (dedicated to the memory of András Szilágyi)

Insulin, to measure or not to measure – PRO

Katalin Nas (HU)
Endocare Institute Ltd.

Context

Insulin plays an important role in the regulation of female reproduction. It has significant effect on hormon production, has major influence on the hypothalamo – hypophyseal - ovarian axis, oocyte maturation, endometrial function and influences the implantation window.

Objectives

Because of its diversified action insulin is an often evaluated parameter, in order to set the diagnosis of hyperinsulinaemia. Due to heterogen phenotypes absolute values of insulin can be only used in case of fasting insulin. Insulin levels evaluated during OGTT can be correlated as absolute values and as ratios of insulin and glucose levels, ratios of insulin and insulin levels measured at different points of OGTT.

Results

The dinamics of insulin secretion can be defined by the shape of the insulin curve. The duration of insulin action can be measured directly, the insulin sensitivity of different tissues can be evaluated by glucose and insulin ratios. More and more information reveals that both reduced insulin sensitivity and impaired insulin secretion can lead to hyperinsulinaemia influencing reproductive function.

The shape of insulin curves correlates with the increased risk of developing type 2 diabetes mellitus. This information can be useful in diagnostic approaches of impaired beta cell fuction.

The methodology of insulin measurements improved significantly, though ADA still did not standardize laboratory techniques. Implementation of OGTT is accurately regulated by WHO which facilitates the reliability of defining hyperinsulinaemia.

Conclusions

Considering the different metabolic states during the menstrual cycle performing tests at appropriate moments eliminates possible inaccuracies of insulin determination due to altering hormonal states.

Symposium organized by HSGE- Hungarian Society of Gynecologic Endocrinology (dedicated to the memory of András Szilágyi)

Vitamin D and pathology in pregnancy

Szabolcs Várbíró (HU), Katalin Nas (HU), László Tűű (HU), Evelin Ábrahám (HU), Valentina Bíró (HU), Dóra Gerszi (HU), Eszter Horváth (HU)

[Várbíró] [Ábrahám] [Bíró] [Gerszi] [Horváth] Semmelweis University, [Nas] [Tűű] Endocare

Background

It is known that vitamin D deficiency might have a negative influence on pregnancy and pregnancy outcomes.
We aimed to study the possible correlations between serum vitamin D levels and changes in carbohydrate metabolism (gestational diabetes - GDM), thyroid function, maternal weight gain/changes, and the offspring's somatometric parameters.

Methods

Changes in maternal serum vitamin D levels were evaluated praeconceptionally and followed each trimester of the pregnancy. Administered vitamin D doses were corrected in order to reach optimal serum vitamin D levels (100-125 nmol/l) each trimester considering body weight and thyroid function.

Results

Serum vitamin D level has an impact on blood glucose level, serious deficiency might cause GDM and a larger weight gain.
Beyond changes in carbohydrate metabolism, we collected data on possible changes in thyroid function, frequency of thyroid disorder, corpus luteum function in the first trimester, body weight changes and blood pressure.

Conclusions

Upon our results seems to have an increase in vitamin D requirement, which rise insufficiency of fix dose replacement. Our results suggest that fix dose vitamin D replacement is not able to maintain optimal serum vitamin D levels and adjusted vitamin D supplementation has benafitial effect on both maternal and neonatal outcomes.

Symposium organized by HSGE- Hungarian Society of Gynecologic Endocrinology (dedicated to the memory of András Szilágyi)

Extremely high AMH level-what is behind?

Jozsef Zeke (HU)
Budai Meddőségi Centrum

Context

The role of AMH levels in predicting reserve ovarian capacity has been already well known since the development of the AMH assay around twenty years ago. Decreased serum AMH levels just like fecundity seems to correlate with maternal age. Another very well known fact is that higher AMH levels are often associated with PCO syndrome. During routine infertility diagnostics, the lecturer has encountered the problem of extremely high AMH levels and has noticed that little is known about its clinical significance and the topic seems to be understudied.

Objective

During this framework, the author has also found some other really interesting and less known facts apart from the detection of extremely high AMH, like the possible use as a predictor of twin pregnancy, and its value in progestin-primed ovarian stimulation (PPOS) protocol. Its value has been already well studied in gonadotropin-releasing hormon agonist and antagonist treatment protocols. Some authors also suggest that AMH levels can be the predictor of the time of menopause in women. AMH in itself seems to be a kind of a strong marker of folliculomas. According to WHO, by 2030 in every year 1,4 million women of childbearing age will be diagnosed by cancer and the AMH's possible prediction values could be used for iatrogen gonadotoxic treatments. The lecture also tries to review the advantages of AMH measurement in fertility preservation techniques. There are some encouranging results about its new application in recombinant form in the field of oncotherapy, delineating a possible new prosperous and innovative treatment.

Methods

The author has aimed to review all known facts about extreme high AMH levels, and tried to summarise of all recent academic research and has realised that little is known about AMH levels above 'normal' ranges. The other point is, that the levels considered to be 'normal' are not yet clarified and agreed on by the experts.

Patients

Two cases will be presented briefly in the lecture, in both cases oncological diseases stood behind the extreme high serum AMH levels.

Conclusions

The lecturer has concluded that it is very important to clarify the differences between ultrahigh and extremely high AMH levels. Less is known about women with extremely AMH levels, but it can be clearly seen by several studies, that it is associated with significantly lower live birth rate, so further studies needed to asses reproductive outcomes.

Updating treatments in reproductive medicine (organized by ESG European Society of Gynecology)

The role of Vitamin D in reproductive medicine

Mark Brincat (MT)
University of Malta. Dept of O&G

Vitamin D is mainly synthesised in the subcutaneous fat from cholesterol under the action of the incident electromagnetic rays from sunlight. Only 10% of Vitamin D can be obtained from dietary sources. It should therefore be correctly described as a hormone. Vit D and its metabolites has a multi systemic effect and this is not compromising since its role in Calcium metabolism is crucial to the function of many systems including cell function. (Kinuta et al., 2008; Anagonistis et al., 2013).
In reproduction various roles are increasingly being ascribed to Vitamin D.
Obstetrics data suggests an association between Vitamin D deficiency and small for gestational age, pre-eclampsia, pre term birth and gestational diabetes (De Leo V, Cappelli V. et al., 2018; Aghejefari F. et al., 2013). Some evidence also exists for an increase in vaginal infection rate associated with Vit D deficiency.
Prenatal Vitamin D supplementation is being recommended by a number of organisations including the RCOG at present.
The debate on the required dose is still an open one but as more reliable SERM assays are developed, the target population at risk can be tested and an aim to have a serum Vitamin D level within the normal range, albeit quite a coincidence can be made.
In gynaecological endocrinology, low vitamin D Levels have been associated with an increased likelihood of the development of fibroid. Low vit D levels have also been associated with endometriosis (Mijashita et al., 2016;
Pagliardini et al., 2015). Vitamin D has been shown to stimulate the ovarian synthesis of ovarian sex steroids and to maintain uterine receptivity.
In addition, the most severe PCO group in our study has been shown to be the one with Vit D deficiency, and a low level of Vit D has been associated with infertility due to PCOS and endometriosis (Anagnostis P et al., 2013).
In postmenopausal osteoporosis, as in any osteoporosis, low vitamin D levels (<50nmols/l or (<20 ng/ml) has been shown to play a major part. The dose of replacement is crucial as is its combination with adequate calcium intake.
In men, low Vitamin D levels have been related to several poor semen parameters and ongoing studies are looking at the relationship and the role of Vitamin D supplementation (Azizi et al., 2018; Juerailetibelie et al., 2019)

Conclusion

All studies have two problems in common, namely ensuring that the correct dose of Vitamin D supplement is given as well as establishing the role of additional and sufficient vitamin D intake. Ensuring that current and accurate Vitamin D assays are in place and confirmation of the normal serum Vitamin D ranges are essential.

Updating treatments in reproductive medicine (organized by ESG European Society of Gynecology)

Aromatase inhibitors (AOI) in ART

Sven Skouby (DK), Nicholas Macklon (GB), Agnieszka Warzecha (DK)
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Infertility is defined as the inability of conception after one year of regular sexual activity without using any contraception methods. It is estimated that around 10-15% of sexually active couples are affected by this problem. The assisted reproduction technics (ART) can be used for the treatment of infertility. Controlled ovarian stimulation (COS) might be required to improve ovulatory problems or increase the number of mature oocytes per cycle. One of the medications used for ovulation induction (OI) is the clomiphene citrate (CC), which leads to successful ovulation rates in most cases (up to 90%). Despite the high ovulation rates achieved with CC the pregnancy rates are still disappointing, varying between 35-40%. This can be attributed to the peripheral antiestrogenic effects of CC. The aromatase inhibitors (AOI), which have letrozole as its main representative, have been increasingly used over the past years. It does not have the deleterious effects that CC does in the endometrium. Letrozol reduces circulating estrogens by preventing aromatization of androgens in the granulosa cells. Mitwally and Casper have used letrozole for OI in patients with previous resistance to CC and obtained success in 75% of cases (1). A study presented by Biljan et al (2005) in the annual conference of the American Society of Reproductive Medicine (ARSM) showed that letrozole use was associated with a high risk of cardiovascular and musculoskeletal malformations in the newborns (2). However, the study some methodological problems such as the heterogeneity between the two compared groups. Studies subsequently published showed no increase in congenital anomalies rates in newborns of patients who conceived after letrozole use for OI. Letrozole is also an established adjuvant in ovarian stimulation for fertility preservation in breast cancer patients, but its general use in COS protocols for IVF is limited. However, there is growing interest in its potential value as an adjuvant to gonadotropins via limiting the supra-physiological rise in estrogen, and thereby reduce the risk of ovarian hyper-stimulation syndrome and the negative impact on endometrial receptivity. Furthermore, it may improve response to gonadotropins in those women with reduced ovarian reserve. However, such a disruption of sex steroid synthetic pathways may have detrimental effects on the oocyte and clinical outcomes. This presentation focus on the functional endocrine changes in normal ovulatory women during COS with letrozole intervention.

1. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001 Feb;75(2):305-9.
2. Biljan MM, Hemmings R, Brassard N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. Fertil Steril. 2005 84 Suppl 1.10–231

Global challenges in women's health (organized by IAHR International Academy of Human Reproduction)

Should oral hormonal contraception still be used in the perimenopause?

Martin Birkhaeuser (CH)
University of Berne, Switzerland

Fertility and age

Fertility declines in with age. Although spontaneous pregnancy is rare after age 50, an effective contraception is required until menopause to prevent an unintended pregnancy. Women over 40 should be offered emergency contraception after unprotected sexual intercourse, if needed.

IUD's

Most guidelines support the extended use of the copper intrauterine device until menopause when inserted at age 40 or over. They also support the extended use of a Mirena® levonorgestrel intrauterine system (LNG-IUS) for contraception until the age of 55 if inserted at age 45 or over. Mirena® may be used with estrogen for endometrial protection (to be changed every 5 years).
Progestogen-only contraceptives: Progestogen-only pills (POP) and progestogen-only implants (IMP) are not associated with increased risks of venous thromboembolism (VTE), stroke or cardiovascular disease (CVD). Women using depot medroxyprogesterone acetate (DMPA), but not POP and IMP, experience initial loss of bone density due to the hypoestrogenic effects of DMPA.

Combined oral contraception (COC)

Smokers should be advised to stop CHC at age 35 as this is the age at which excess risk of mortality associated with smoking starts to become clinically significant.

Non-smokers

COC with ≤30µg ethinylestradiol (EE) should be considered first-line COC prepa-rations for women over 40 due to the potentially lower risks of VTE, CVD and stroke compared to formulations containing higher doses of EE. COC with LNG or norethisterone should be conside-red first-line COC preparations for women over 40 due to the potentially lower VTE risk compared to COC formulations containing other progestogens. CHC may help to maintain BMD compared with non-use of hormones in the perimenopause.
Women aged ≥ 50 should stop taking CHC and use an alternative, safer contraceptive method.

Oral Presentations

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

The effect of autoimmune thyroid disease on the ovarian reserve of women

Yulia Absatarova (RU), Olga Grigoryan (RU), Robert Mikheev (RU), Natalia Krasnovskaya (RU), Irina Yarovaia (RU), Elena Andreeva (RU), Ivan Dedov (RU)

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Context

Several studies have shown a likely relationship between autoimmune thyroid diseases and reproductive disorders in women, but the results are contradictory, and the pathogenetic mechanisms are not clear.

Objective

To compare the ovarian reserve in healthy women of reproductive age with antithyroid antibodies (ATA) and in healthy women of reproductive age without ATA.

Methods

The following markers of the ovarian reserve were determined on the 2nd-4th days of the menstrual cycle: serum levels of anti-Müllerian hormone (AMG), inhibin B, FSH, LH, estradiol, testosterone and progesterone. The number of antral follicles and the volume of the ovaries were examined by ultrasound.

Patients

70 healthy women of reproductive age in the state of euthyroidism (from 18 to 38 years old).

Interventions

Participants were divided into equal groups (n = 35) depending on the status of the presence of antithyroid antibodies (AT-TPO, AT-TG).

Main outcome measures

To determine the predisposition to premature ovarian failure, an analysis of the number of CGG repeats in the FMR1 gene was performed.

Results

The levels of estradiol and testosterone significantly differed but the differences were not clinically significant. All evaluated parameters were within the normal range, the main markers of the ovarian reserve (levels of AMG and inhibin B, the number of antral follicles) remained in the normal range. An increase in the number of repeats of CGG in the FMR1 gene was not detected in any of the participants in the study.

Conclusions

In healthy reproductive aged women, the status of ATA does not have a direct effect on the ovarian reserve. This work was supported by the Russian Science Foundation under Grant №17-75-30035.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

A comparison of progestogens plus GnRH agonist versus progestogens only in luteal phase support in IVF women: a retrospective single centre experience

Jojinah Vindah Alexander (MY), Muhammad Azrai Abu (MY), Mohd Faizal Ahmad (MY), Abdul Kadir Abdul Karim (MY), Mohd Hashim Omar (MY)

Universiti Kebangsaan Malaysia

Objectives

To evaluate effects of the addition of single-dose GnRH agonist to the routine progestogens use for luteal phase support on IVF outcome as compared to progestogens only.

Methods

This is a retrospective study on selected patients who underwent IVF treatment under MAC (Medically Assisted Conception) Unit, University Kebangsaan Malaysia Medical Centre for the period of June 2015-June 2018. Their medical records were reviewed, and data analysed. The inclusion criteria were all patients who underwent ICSI and were given progestogens plus GnRH agonist or progestogens only as luteal phase regime. Patients with different luteal phase regime, frozen embryo transfer and medical records with missing data were excluded. The pregnancy outcomes measured included biochemical pregnancy rates, clinical pregnancy rates, live birth rates and miscarriage rates.

Results

A total of 393 patients were included. A total of 222 patients were given luteal phase support with progestogens and GnRH agonist, whereas 171 patients served as control were given progestogens only. The GnRH agonist group showed higher biochemical pregnancy rate (47.7% vs 44.4%,), clinical pregnancy rate (25.7% vs 23.4%) and livebirth rate (24.3% vs 22.2%) respectively but not statistically significant. The rate of miscarriage among GnRH agonist group was lower (4.5% vs 9.4%) compared to progestogen group alone. Nonetheless, the OHSS rate was slightly increased in GnRH agonist group (4.5% vs 3.5%) despite using mild stimulation protocol.

Conclusions

Luteal phase support with addition of GnRH agonist in standard progestogen support was found to be beneficial in overall IVF outcome.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Prolactin and prolactin receptor expression on the adrenal of hyperprolactinemic mice treated with estrogen and progesterone

Vinicius Cestari do Amaral (BR), Tommaso Simoncini (IT), Priscilla Ludovico da Silva (BR), Edemund Chada Baracat (BR), Jose Maria Soares-JR (BR)

[Cestari do Amaral] UNIP / UNINOVE, [Simoncini] Universita di Pisa, [Ludovico da Silva] UNINOVE, [Chada Baracat] [Soares-JR] FM - USP

Objective

To evaluate the effects of metoclopramide-induced hyperprolactinemia on prolactin and prolactin receptor expression in mice treated with estrogen and progesterone.

Methods

A total of 12 animals with intact ovaries were allocated to two groups: G1 (saline solution) and G2 (metoclopramide). A total of 30 oophorectomized animals was randomized to five subgroups: G3 (control), G4 (metoclopramide), G5 (metoclopramide+17β-estradiol), G6 (metoclopramide+progesterone), and G7 (metoclopramide+17β-estradiol+progesterone). The drugs/hormones and the vehicle were administered subcutaneously as previously described in the literature. After 50 days, immunohistochemical analysis of the adrenal gland was performed using the expression index (EI) calculation method.

Results

All groups expressed prolactin and prolactin receptor; however, both the intensity and the frequency of labeled cells were heterogeneous. Concerning the prolactin receptor (PRLR), the area fraction of labeled cells varied from 1 (0%-10%) to 3 (> 50%). Based on the mean immunostaining intensity, G2 and G4 showed strong expression; G6 and G7 presented a mild reaction; and G1, G3, and G5 exhibited a weak reaction. Concerning prolactin (PRL) expression, the area fraction of labeled cells varied from 1 (0%-10%) to 3 (> 50%), and groups G6 and G7 showed a strong reaction; G2, G4, and G5 showed a mild reaction; and G1 and G3 exhibited a weak reaction.

Conclusion

Our data suggest that metoclopramide-induced hyperprolactinemia may increase prolactin receptor expression in the adrenal gland of mice. Furthermore, hyperprolactinemic animals treated with progesterone alone or in association with estrogen may have an increased prolactin expression.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Gender differences on the expression of the HLA-G immune checkpoint molecule and of the BRAF oncoprotein in papillary thyroid carcinoma

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[Donadi] [Bertol] [Sadissou] [Dias] [de Figueiredo-Feitosa] [Collares] [Conti de Freitas] [Garcia Soares] [Serafini] [Zanini Maciel] University of Sao Paulo, [Goes de Araújo] [Nogueira Silbiger] Federal University of Rio Grande do Norte

Background

Papillary thyroid carcinoma (PTC) is a common endocrine malignant neoplasia primarily affecting women, which may eventually present an aggressive behavior. PTC aggressiveness has been associated with an immunosuppression microenvironment and oncogenes. The oncogenic 1799 T>A (V600E) transversion in the BRAF gene has been associated with poor prognosis; however, little information is available on BRAF expression profile in PTC. Additionally, the tumor expression of the human antigen leucocyte (HLA)-G may be associated with poor prognosis due to its ability to inhibit Natural killer and CD8+ T cells. The exact mechanisms by which HLA-G gene expression is regulated are not completely understood; however, sexual hormones may modulate HLA-G expression.

Objective

To evaluate the expression of HLA-G and BRAF molecules in PTC specimens, and to detect the levels of soluble HLA-G (sHLA-G) in PTC plasma, stratified according to patient gender.

Methods and patients

The expression profile of HLA-G and BRAF was evaluated in PTC specimens using immunohistochemistry (36 men and 147 women), and immunoreactivity was stratified into two categories: ≤50% (low expression) or >50% (high expression). The chi-square test was used for statistical analysis. sHLA-G levels were determined by ELISA in plasma of PTC patients collected before thyroidectomy and data were analyzed using Mann-Whitney test. P values below 0.05 were considered significant.

Results

Different from normal thyroid samples, PTC specimens frequently expressed both HLA-G (67.96% of specimens) and BRAF (62.43%). There was a positive correlation between HLA-G and BRAF expression ($r=0.4387$, $P<0.001$), and the expression of both molecules was increased in female patients ($P=0.0110$ and $P=0.0353$ respectively) compared to males, irrespective of patient age (age cutoff: 45 years old). Plasma levels of sHLA-G were increased in female patients when compared to males; however, significance was not reached. No association was observed between plasma sHLA-G levels and the magnitude of HLA-G and BRAF in PTC specimens.

Conclusion

Considering that HLA-G can inhibit the immune response and considering that BRAF is a cancer-associated marker, the concomitant increased expression of both markers in PTC microenvironment of female patients may contribute to the development of thyroid malignant lesions in women.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Premature ovarian insufficiency and the risk factors in Uzbek women

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Centre of Endocrinology

Nowadays in the world, the premature ovarian insufficiency (POIS) is considered as an urgent medical and social problem. Special attention is paid to research to determine the diseases of women of childbearing age, improvement of methods for early diagnosis, treatment and prevention based on immunogenetic research. In this area, the priority areas of scientific research remain the identification of heterogeneous causes of PNT, genetic, enzymatic, autoimmune, infectious-toxic, iatrogenic and psychological factors, the determination of changes in its biochemical and immunological parameters. Early prediction of gene mutations for the purpose of prevention are the actual problems of specialists in this field.

The aim of the study was to determine the clinical and genetic markers while predicting premature ovarian failure in women of Uzbekistan.

The object of the study was the screening the data of 3421 women of fertile age and clinical, laboratory, medical and genetic examination of 85 patients with POF.

Results

A group of 454 women with amenorrhea up to 40 years of age (13.3% of the total number of women screened and 58.3% of the number of women with amenorrhea) were identified among 3421 questionnaires. Then 85 has a high level of FSH (over 25 IU / L, 61.5 ± 2.3 IU / L), which accounted for 10.9% (85/779) of the total number of women with amenorrhea and 2.5% of the total the number of respondents (85/3421). Women with PNY under the age of 20 make up 9.1%, and women over 36 years old - 34.1%.

When analyzing the nature of reproductive function, it was found that 35 (41.2%) of 85 patients with PNY had a history of childbirth, 12 (14.1%) had abortions Of 85 patients with PNY, 13 (15.3%) women were noted primary infertility, and in 12 (14.1%) women with secondary infertility. The average level of LH and FSH in patients with PAI was significantly higher, amounting to 41.2 ± 2.1 and 31.0 ± 1.6 IU / l, respectively.

The estradiol concentration was lower than the standard values and amounted to 70.4 ± 4.2 pg / ml. In a molecular genetic study, 83 samples were genotyped. Homozygous mutation A / A of the rs 6166 polymorphism of the FSHR gene was almost 2 times more common in the main group and amounted to 23.6% versus 10.7%. When analyzing the rs 6165 polymorphism of the FSHR gene, there was a 2-fold increase in the frequency of this genotype in patients of the main group (14.6%) compared with the control group (7.1%).

As a result of the study of gene-gene interactions of allelic variants of the rs6165 polymorphism and rs6166 of the FSHR gene, we found that the combination of functionally unfavorable genotypes of the rs 6165 + rs 6166 polymorphisms of the FSHR gene significantly increases the risk of the formation of a stump ($\chi 2 = 4.1$; $P = 0.04$; OR = 3.7; 95% CI0.98–14.05)

Conclusions

The frequency of occurrence of PNI in Uzbekistan is 2.5%. Clinical and hormonal markers for prediction of PSI is an increase in FSH levels above 25 IU / L ($r = 0.61$; $P < 0.01$), a decrease in estradiol values below 75 pg / ml ($r = 0.47$; $P < 0.01$), decrease in the number of antral follicles (less than 6 pcs.) during ultrasound examination ($r = 0.75$; $P < 0.01$). As a result of the study of gene-gene interactions of allelic variants of the rs6165 polymorphism and rs6166 of the FSHR gene, we found that the combination of the functionally unfavorable genotypes of the rs6165 + rs 6166 polymorphisms of the FSHR gene significantly increases the risk of STI formation by 3.7 times.

It is proved that the most favorable / projection genotype for FSHR G> A rs6166 is the GG genotype, while the AA genotype is risky.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Comparison of bone, metabolic and anthropometric changes in young women with premature ovarian insufficiency or complete androgen insensitivity syndrome with removed gonads using oral estradiol valerate, transdermal estradiol or oral ethinylestradiol

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Context.
In young women with hypergonadotropic amenorrhea, hormonal therapy (HT) is mandatory as it plays a significant role in bone protection and in the prevention of cardiovascular disease and mortality. There is still little evidence on the optimal dose, regimen and type of HT in young women with absent hormonal production and in particular data are still lacking on oral administration of estradiol valerate

Objectives
To compare changes in bone, metabolic and anthropometric parameters in young women with hypergonadotropic amenorrhea (premature ovarian insufficiency [POI] and complete androgen insensitivity syndrome [CAIS] with removed gonads) undergoing different hormonal treatments (oral estradiol valerate, transdermal estradiol, oral ethinylestradiol, with or without progestin or no treatment).

Methods
In this retrospective observational pilot study, bone, body composition and anthropometric parameters were assessed in 40 young women.

Patients
Fifty-five percent of enrolled patients were CAIS while 45% were POI (20% idiopathic or iatrogenic POI and 25% Turner syndrome). Mean age at the time of the first DXA scan (t0) was 23,8 ± 5,5 years (range: 15-35 years).

Results
At t0 the whole cohort presented some impairment of bone mineral density in particular at the lumbar level. Only 5% of patients presented with normal BMD in all bone sites, while 75% and 20% presented with osteopenia or osteoporosis, respectively, in at least one bone site. The follow-up DXA scan (t1) was performed 22.1 ± 9.2 months after t0 and showed that the treatment with oral estradiol valerate was able to significantly increase lumbar, femoral and total body BMD (p=0.017, p=0.04 and p=0.039 respectively). Transdermal estradiol was associated with an increase in femoral and lumbar BMD but the increase was statistically significant only in the lumbar site (p=0.009). Oral ethinylestradiol was associated with further impairment in femoral BMD while lumbar and total body BMD remained stable. No significant changes in anthropometric and metabolic parameters were noted throughout the treatment period.

Conclusions
Our results suggest that in young women with POI or CAIS oral estradiol valerate or transdermal estradiol are both associated with greater improvement in bone health if compared to oral ethinylestradiol.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

The thyroid function in women of reproductive age after kidney transplantation

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Belarusian State Medical University

Context
Chronic kidney disease is associated with various dysfunctions of the thyroid gland due to disorders of the synthesis, metabolism and clearance of thyroid hormones. TSH increasing and decreasing of the free fractions are significantly associated with lowering GFR and may serve as a predictor of mortality. Kidney transplantation (KT) is a golden standard in treatment of ESRD and is vital for improving the longevity and quality of life in these patients.

Objective
To investigate thyroid function in women of reproductive age after kidney transplantation.

Methods – Patients
The study included 71 women. A study group (SG) consisted of 39 women (the median age was 36 yrs). Inclusion criteria for SG were: female, reproductive age (18-49 yrs), single episode of KT in State Institution "Minsk Scientific and Practical Center of Surgery, Transplantology and Hematology" during 2010-2018, adequately graft function. Before KT all patients received hemodialysis (duration Me 16.5 [7.0; 36.0] mo.). The period from the moment of KT to blood taking to study the level of hormones was 36.5 [24.0; 96.0] mo. The control group (CG) consisted of 32 healthy women (the median age was 29 yrs). Serum levels of TSH, fT4, anti-TPO were examined by ELISA in all patients.

Results
Among the women of CG no abnormalities were found in the studied hormones (anti-TPO 10.0 [5.0; 70.0] ME/ml vs 8.0 [5.0; 11.0] ME/ml), TSH (2.11 [1.6; 3.3] mmol/ml vs 1.93 [1.4; 3.2] mmol/ml), fT4 (13.10 [11.8; 13.8] pmol/L vs 13.45 [11.7; 14.6] pmol/L). There were no differences between the total SG and the CG for the estimated parameters. Patients belonging to SG were further divided in two groups according at the observation period after kidney transplantation. The 1st group consisted of patients with observation period less than 37 mo. The 2nd group consisted of patients with observation period more than 37 mo. respectively. The patients with longer observation period demonstrated decrease in TSH (1.61 [1.10; 3.21] mmol/ml vs 2.14 [1.60; 3.20] mmol/ml) and increase in fT4 (14.10 [12.45; 14.60] pmol/L vs 13.30 [11.0; 14.60] pmol/L) in comparison with the 1st group within normal range.

Conclusions
We identified that the thyroid function in women of reproductive age after kidney transplantation gradually improves. The results have shown that serum levels of TSH decreased gradually and serum levels of fT4 increased gradually within the normal range. No thyroid autoimmunity was detected.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

The impact of total body fat mass with its distribution to the trunk, in thyroid hormone levels, after complete weight restoration and menstrual recovery or not, in adolescents with Anorexia Nervosa

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Context-Objective

To determine the role of total body fat mass with its distribution to the trunk, in thyroid hormone levels, after complete weight restoration and menstrual recovery or not, in adolescents with Anorexia Nervosa.

Methods-Patient(s)-Intervention(s)

Prospective study of 60 adolescents with Anorexia Nervosa and amenorrhea. Anthropometrics, body composition measured with dual-energy x-ray absorptiometry (DXA) and hormonal studies, were obtained at the beginning and at complete weight restoration, independently of menstrual recovery (Group A) or not (Group B).

Main outcome measure(s)-Result(s)

Free Triiodothyronine (FT3), Free Thyroxine (FT4) and Thyroid-Stimulating Hormone (TSH) levels were statistically significantly higher ($p<0.001$) at the end of the study, compared with time at first attendance for both Groups. At weight restoration, a statistically significantly positive correlation was found between total body fat mass (Kg and %), trunk fat mass (Kg and %) and FT3, FT4 for Group A and Group B adolescents. At the same time, trunk / extremities fat ratio was found to be statistically significantly positively correlated with FT3 ($r=0.586$, $p<0.001$) and FT4 ($r=0.512$, $p<0.01$) but not with TSH in girls who recovered their menses, in contrast with adolescents who remained amenorrhoic.

Conclusions

Total boy fat mass with its distribution to the trunk is statistically significantly positively correlated with FT3 and FT4, in adolescents with Anorexia Nervosa, who completed restored their weight and recovered their menses.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

The incidence of subclinical hypothyroidism in pregnant women

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Aim

Investigating the incidence of subclinical hypothyroidism in pregnant women, an asymptomatic condition characterised by elevated values of blood TSH, while the values of the thyroid hormones remain within normal range, using a thyroid ultrasound and a laboratory analysis of TSH and fT4 in a gynaecological clinic in Zadar, Croatia, and any occurrence of obstetric and neonatal complications.

Method

In the period from 01/11/2018 to 01/12/2019, thyroid ultrasounds and laboratory results of TSH and thyroid hormones from 305 pregnant women out of 6250 registered patients, which is 4.88%, discovered 21 pregnant women with irregular laboratory results, which is 0.34% of all the patients. The thyroid ultrasounds have determined changes in the echogenicity, size, and the shape of the thyroid gland, and the laboratory values indicated deviations from the normal TSH levels, which are 2.500 in the first 12 weeks of pregnancy, and up to 3.000 after that, (HDGO recommendation), and fT4 values under 20. The participants were of various ages, parity, and weeks of pregnancy. The TSH value of the new-borns was also analysed through screening for congenital hypothyroidism.

Results

Ultrasound and laboratory selection of TSH and thyroid hormones in the above period has identified 21 pregnant women with altered ultrasound and laboratory TSH, out of 305 registered pregnant women, which is 6.89%. TSH for other 284 pregnant women was normal, which is 93.11%. Among the 21 pregnant women with altered ultrasound and laboratory TSH, 14 were cases of subclinical hypothyroidism, which is 66.66%, 4 Hashimoto's thyreoditis-19.04% (antibody proof), 3 hyperthyroidism-14.29%. All the pregnant women with elevated TSH values were prescribed levothyroxine natrium. After the children were born, they had no congenital hypothyroidism or elevated TSH.

Conclusion

The analysis of the results from my patients within the relevant period indicates that subclinical hypothyroidism has the highest incidence. After the levothyroxine natrium therapy, there were no difficulties during the pregnancy or delivery, or any TSH deviations for the new-borns.

*TSH-thyroid stimulating hormone, *fT4-free thyroxine, *HDGO-Croatian Society of Gynaecologists and Obstetricians

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Subclinical hypothyroidism in pregnancy: disease versus TSH pulsatility

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Context

There is no consensus regarding the upper "cut off point" for TSH in pregnancy, so concentrations above 2.5 mU/L (Endocrine Society, 2012) or 4.0 mU/L (American Thyroid Association, 2017) for 1st trimester are suggested to be indicative for subclinical hypothyroidism. Furthermore, the impact of pulsatile TSH secretion during pregnancy has not been assessed.

Objective

To assess whether physiological (pulsatile) TSH secretion might erroneously lead to a diagnosis of subclinical hypothyroidism in pregnancy.

Patients

110 healthy pregnant women, age 30.2±6.0 years, at 9.9±2.4 weeks of gestation.

Intervention & methods

We assessed baseline concentrations of free T4, free T3, the titre of anti-thyroid peroxidase (aTPO) antibodies as well as TSH concentrations at 30 minute intervals (between 7.00 and 9.00 hours, i. e. during five consecutive measurements).

Results

Elevated titre of aTPO antibodies was found in 11 (10%) patients. Mean TSH concentrations were 1.62 mU/L, and varied by 23.74% depending on dispersion between the highest and the lowest TSH concentrations. Taking into account the highest TSH out of five consecutive measurements, concentrations of TSH>2.5 mU/L, or above 4.0 mU/L were found in 23, and 10 patients, respectively. In contrast, when the lowest TSH value was considered, then concentrations of TSH>2.5 mU/L, or >4.0 mU/L were found in 14 and 4 patients, respectively. This discrepancy was even more pronounced in aTPO-negative patients (21 versus 8 patients (61.9%), for TSH>2.5 mU/L, and six versus one (83.3%), for TSH>4.0 mU/L).

Conclusions

In a significant number of patients, diagnosis of subclinical hypothyroidism could be erroneously made not as a result of "disease", but as a result of physiological variation in TSH concentrations. It remains to be established, whether a single TSH measurement is enough to diagnose subclinical hypothyroidism in pregnancy.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

OvAge - early prediction of premature ovarian insufficiency

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Context

Basing on the 2019 global meta-analysis, prevalence of premature ovarian insufficiency (POI) reached 3.7% among women under 40 years old. Revealing the POI initial forms will allow for increasing the chance of pregnancy with own oocytes. Development of a widely available and highly sensitive and specific marker for assessing ovarian reserve based on biochemical and 3D-ultrasound data remains relevant, and ovarian age validation based on a mathematical model of Venturella and co-authors has not been validated.

Objective

To determine the ovarian age in female patients with occult, biochemical, and full forms of POI based on the use of the mathematical model of Venturella and co-authors.

Methods

A prospective cohort study involved 194 women, at an average age of 31.6±4.9 years. All patients underwent measurement of FSH, AMH on the 2-3rd day of menstruation, AFC in the entire volume of the ovaries, VI, FI through a 3D ultrasound examination.

Results

the main group (group 1) involved 134 women with AMH levels of less than 1.1 n /ml. Group 1A comprised 33 female patients with a POI occult form (FSH 8.7 ± 0.5 IU/l, AMH 0.9 ± 0.2 ng/ml, AFC 8.5 ± 1.2, VI 3.6 ± 0, 5, FI 26.2 ± 1.6), 1B - 46 female patients with the POI biochemical form (FSH 21.2 ± 0.9 IU/l, AMH 0.2 ± 0.03 ng/ml, AFC 3.9 ± 0.6, VI 5.2 ± 0.6, FI 29.3 ± 1.1), 1C - 55 female patients with the entire POI form (FSH 86.5 ± 4.7 IU/l, AMH 0.2 ± 0 03 ng/ml, AFC 1.6 ± 0.3, VI 1.7 ± 0.2, FI 22.4 ± 0.9). The comparison group (group 2) comprised 59 fertile women with regular menstruations (FSH 6.9 ± 0.2 IU/l, AMH 4.9 ± 0.4 ng/ml, AFC 29.6 ± 1.3, VI - 10,4 ± 0.6, FI - 34.2 ± 0.5).

To determine OvAge, we applied the following equation: 48.05-3.14*AHM+0.07*FSH-0.77*AFC-0.11*FI+0.25*VI+0.1*AMH*AFC+0.02*FSH*AFC. Average OvAge values in group 1A were 39.4 ± 1.2 years, while their chronological ones were 32.5 ± 1.2 years (p=0.002). In group 1B and 1C, OvAge was 45.6 ± 0.3., 52.3 ± 0.8 years, against 34.0 ± 0.7, 33.1 ± 0.8 years, respectively (p=0.0000001, p=0.000000037). In group 2, OvAge 28.9 ± 0.4 years coincided with the chronological one 27.7±0.4 years (p=0.07).

Conclusions

OvAge, determined on the basis of a combination of hormonal and 3D-ultrasound markers for ovarian reserve assessment, is a reliable POI predictor, regardless of their clinical form. Thus, chronological age is not always a reliable marker for assessing ovarian reserve.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Diagnostic approach to a rare case of primary amenorrhea with 46,XX gonadal dysgenesis and absent uterus in an adolescent girl

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Context
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Objective
To report a rare case of bilateral ovarian dysgenesis and absent uterus with normal female karyotype and to discuss the correct diagnostic approach for primary amenorrhea.

Methods
Case Report.

Patient
A 15-year-old female with complaints of primary amenorrhea, short stature and lack of secondary sexual characteristics.

Intervention
Physical, gynecological, endocrinological and genetic evaluation were done.
Laboratory studies including blood count, biochemical markers including renal and liver function tests and autoimmune markers, pituitary, ovarian and thyroid hormone levels were performed. Analysis of chromosomes in peripheral blood cultures; FMR-1 gene mutation test, FISH analysis of SHOX gene; assessment of bone mineral density, ultrasonography and abdominal MRI were performed for diagnosing associated malformations.

Main outcome measures
Clinical, hormonal, anatomical and genetic features of the patient in response to hormone replacement therapy.

Results
The performed laboratory and imaging studies revealed a hypergonadotropic hypogonadism case with 46,XX karyotype. While normal vaginal pouch (6 cm in length) was observed; ultrasonography and abdominal MRI visualized neither uterus, nor bilateral ovaries. Normal kidney and urinary tract structures was confirmed. The patient received hormone replacement therapy (Estradiol hemihydrate 2mg/d) for three months. During follow up, her breast development was mildly improved (Tanner II), but no axillary and pubic hair growth were observed. A rudimentary uterus (size of 51*20 mm, endometrium thickness 6.5 mm) was detected in transrectal ultrasonography and abdominal MRI. Gestagen challenge test was applied (Noretisteron 10 mg/d along with estradiol hemihydrate 2mg/d) and the patient had her first menstruation lasting for 7 days.

Conclusion
A detailed anamnesis, physical examination and laboratory studies are necessary for early diagnosis and intervention of primary amenorrhea cases. Instead of imaging techniques that don't give reliable results in prepubertal stages, physical examination must be considered for differential diagnosis. Patient follow-up with repetitive imaging strategies after hormone replacement therapy for at least 6 months should be done to avoid unnecessary invasive techniques and false diagnosis.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Novel FSHB mutation leading to isolated FSH deficiency – a rare case report

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Objective

Isolated FSH deficiency is a very rare, autosomal recessive disease caused by mutations in FSHβ gene. Only few case reports have been described in the literature.

Patient

We report 25-years old woman who was admitted to the Endocrinology Department with a suspicion of FSH deficiency. Primary amenorrhoea and impaired pubertal development were firstly diagnosed when patient was 17 years old. Hormonal tests were performed and low concentrations of FSH and estradiol were found, however LH level was elevated. MRI did not reveal any pathological findings in the pituitary region. Treatment with estrogens and then estrogen-progesterone was started and continued for 8 years. Hormonal replacement therapy was withdrawn 7 days before admission to our department. During hospitalization hormonal function tests were performed. Patient did not present any clinical or laboratory signs of hyperandrogenism. FSH and estradiol concentrations were undetectable, while LH level was mildly elevated (19.9 mIU/ml). In the gonadotropin-releasing hormone stimulation test there was no response in FSH concentration. What is more, anti-Mullerian hormone (AMH) concentration was within the range (5.62 ng/ml) and inhibin B level was undetectable low. Next-generation sequencing were performed and novel homozygotic mutation in FSHB gene was found (ENST00000417547c.236-237delTG, protein p.Val79fs). Isolated FSH deficiency was diagnosed.

Conclusion

Clinical picture of FSH deficiency in our patient is similar to those presented in the literature. However, it is worth to notice, that a severe deficiency of FSH was not related with AMH deficiency what is in opposite to conclusions of research studies conducted in patients with isolated hypogonadotropic hypogonadism. Patients with isolated deficiency of single gonadotropin give us a new, important insight into its role in human fertility processes, which are still under investigation.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Prolactinoma and pregnancy: what do we know so far?

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Context
A prolactin-secreting pituitary tumor represents the most common cause of hyperprolactinaemia, leading to central hypogonadism and infertility. In most cases, treatment with dopamine agonists (DA) allows restoration of fertility. However, it still remains a concern about the risk of tumor growth, as well as the effects of the treatment on the developing fetus.

Objective
The aim of this paper is to review the latest information concerning the management of prolactinomas during pregnancy and to present a case of a patient diagnosed with a microprolactinoma and a successful pregnancy, after 7 years of treatment with DA.

Patient
A 31-years old woman is admitted for a follow-up after a successful pregnancy. She was diagnosed with a prolactinoma back in 2010, treated with Carbegoline for 5 years, with no other medical records until 2016, when she was admitted in our clinic for the first time. Prolactin levels were 9863 mUI/ml (102-496) and the MRI examination showed a pituitary microadenoma of 4/5 mm diameter. At the 1 year follow up, in November 2017, the microadenoma had a 7,8/3,9 mm diameter.

Result(s)
In this case, treatment with DA was withdrawn as soon as pregnancy was confirmed. The MRI at 3, 6 and 12 months postpartum showed no changes in tumor size and prolactin levels were normalized without treatment, which still remains a subject that needs further studies. The patient breastfed for 1 year and the baby was in perfect health.

Conclusions
Management of prolactinomas in pregnancy still remains a challenging subject among endocrinologists. Also, it is important to note that many patients with prolactinomas become normoprolactinaemic after pregnancy, even without treatment.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Hormonal changes in men with “empty sella” syndrome

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Purpose of the study

Explore the hormonal changes in men with ‘empty sella’ syndrome (ESS).

Material and methods

We examined 29 men with PTSD syndrome, mean age 39±2.29 years, of which the primary “empty” selle 6 men; secondary-11 men; emerging-12 men. The clinical examination included medical history, physical examination, brain MRI study, hormonal study.

Results

In patients with ESS detected subclinical hypothyroidism, characterized by a significant increase ($p < 0.001$) TSH levels, which amounted to 5.8±0,24mME/l at normal rates triiodothyronine and thyroxine (2,6±0,1nmol/l and 90, 5±4,3nmol/l, respectively). PRL level was 12.0±0,6ng/ml, which was significantly higher ($p < 0.001$) of mean values of the control group. Indicators of FSH, LH and testosterone levels were also significantly lower than the values of the comparison group and constitute. Secondary ESS was diagnosed in 11 men, 9 of which have suffered from acromegaly, at 2 determined functionally inactive pituitary tumor (FIPT). The nature of hormonal status in patients with secondary ESS determined view of the treatment. Patients with acromegaly in combination with secondary ESS background radiation therapy as a noted decrease in gonadotropins (FSH equal 0,73±0,03ME/l and LH=0,68±0,02ME/l) and thyroid stimulating hormone (TSH=2,8±0,17mME/l), which had a direct impact on the level of peripheral hormones values were also below the average of the control group. T3 level was 1.9±0,12nmol/L±4,7nmol T4-97/l and testosterone - 3,8±0,2nmol/l. Group emerging ESS were 12 patients. The complaints in these patients were of the nature of neurological disorders. Hormone levels in this group was not determined. In 7 patients with PESS had microadenoma emerging pituitary gland, treatment of DFM and 1 pituitary adenoma (Acromegaly), the treatment of which was conducted DFM in conjunction with radiation therapy. Patients with pituitary microadenomas during treatment with DFM, complicated FESS, significant changes in hormonal levels were observed exception was the level of testosterone, whose figure was significantly lower than the control group and was 8.7±1,2nmol/l.

Conclusions

1. Men with the syndrome of primary ESS revealed subclinical hypothyroidism, and hyperprolactinemia.
2. Significant increase in TSH and PRL, St. T4 decrease observed in men with secondary ESS in the treatment of the combination therapy of the underlying disease (DFM ray + reception).

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

Neurokinin B and nesfatin-1 concentration in patients with functional hypothalamic amenorrhea- preliminary results

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Context
Functional hypothalamic amenorrhea (FHA) is a reversible disorder related to aberration of the pulsatile release of gonadotropin-releasing hormone (GnRH). A large number of neurotransmitters secreted in the central nervous system plays a particular role in the control of the GnRH secretion. Neurokinin-B has essential impact on pubertal maturation and the regulation of reproductive system. Nesfatin-1, similarly, has permissive stimulatory effects on the gonadotropic axis and plays essential roles in the metabolic control of reproduction thus plays a significant neurohormonal signal linking body metabolic status and fertility

Objective
The aim of the study was to evaluate the neurokinin B and nesfatin-1 role in etiopathogenesis of FHA.

Methods
In each patient we assessed hormonal profile: FSH, LH, prolactin, E2, DHEA-S, testosterone, TSH, free thyroxine, fasting glucose and insulin level, we estimated lipid profile and measured BMD in the lumbar spine by dual-energy X-ray absorptiometry (DXA)

Patients
26 FHA patients and 20 healthy age-matched controls were included to the study. The criteria of FHA diagnosis were secondary amenorrhea of at least 3 months duration, E2 serum concentration <30 pg/ml and LH serum concentration <5 IU/l.

Intervention, Main outcome measure
Neurokinin B and nesfatin-1 concentration were measured in FHA group.

Results
There was statistically significant difference in FSH ($p=0.41$), LH ($p<0.001$), E2 ($p<0.001$), TSH ($p<0.001$), fT4 ($p<0.001$), prolactin and fasting insulin concentration ($p<0.001$) between FHA patients and controls. In FHA group mean neurokinin B concentration (257,16 ± 128,03 ng/L) was lower in comparison to healthy controls (639,32 ± 586,38), with statistically significant difference ($p=0.007$). Mean nesfatin-1 concentration (5,51 ± 3,20) was also lower when compared to healthy controls (13,54 ± 15,81), but without statistically significant difference ($p>0.05$). There was no statistically significant correlation between NKB and nesfatin-1 and BMI ($p=0.17$ and $p=0.27$, accordingly) in FHA group. Such correlation was also not observed in control group ($p=0.07$ and 0.11, accordingly).

Conclusions
Patients suffering from FHA have decreased concentration of neurokinin B and nesfatin-1. It is believed, that changes in the secretion of NKB and nesfatin-1 which impair subsequently GnRH release could contribute to etiopathogenetic basis of FHA. However, further studies are required.

Endocrinology and neuroendocrinology: amenorrhea, adolescence and thyroid

The effect of meditation practices on neuroendocrine determinants

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Introduction

Meditation is a complex mental process that involves changes in cognition, sensory perception, emotions, hormones and autonomic activity.

Objective and methods

The aim was to provide a framework of the neuroendocrinological correlates of meditative practices with respect to mental health, stress reduction and hormonal balance. The existing date on neurophysiology with regard to meditative practice was systematically reviewed. Brain function and structure were assessed by functional magnetic resonance imaging (fMRI) and neurochemical related changes were assessed in serum.

Results

Different neurotransmitter system and hormones, including Serotonin, Melatonin, Gaba, Arginine vasopressin, Cortisol, Norepinephrine are affected by meditation practices. Functional brain changes were demonstrated in Prefrontal, Cingulate and Parietal Cortex. Moreover Hyppocampal, Amygdalar and Talamic activity was altered during meditation.

Conclusion

The neurophysiological effects that have been observed during meditative states seem to outline a consistent pattern of changes involving key cerebral structures in conjunction with autonomic and hormonal changes. Meditation has become widely used in combination with other therapies for stress reduction and for variety of physical and mental disorders. Futures studies are necessary to illuminate integrative knowledge of complex neuroendocrine systems.

Prenatal medicine and early pregnancy

A case report of boerhaave syndrome at first trimester of pregnancy and review of the literature

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Context

Boerhaave syndrome is a rare condition characterized with spontaneous rupture of the esophagus and is associated with high mortality rate. It is an urgent situation and requires prompt diagnosis and immediate intervention in order to avoid severe complications, even death. The incidence of Boerhaave syndrome among young pregnant women is very low and usually is associated with hyperemesis gravidarum.

Objective

Our aim is to present a very uncommon case of Boerhaave syndrome at 1st trimester of pregnancy in order to increase the awareness of this condition and report the importance of early diagnosis, correct decision making and management as well as their impact on outcome.

Methods

We conducted an extensive search of the literature using PubMed and search engines (e.g.Google) based on keywords like Boerhaave syndrome, pregnancy, hyperemesis gravidarum.

Patient

We report the case of a 31 -year old G1P0 woman who was admitted to the hospital at 10+4weeks of pregnancy due to severe vomiting and electrolyte imbalance. She suffered from severe depression and, during her hospitalization, her relatives revealed that all the episodes of vomiting were provocative. Despite the close Psychiatric supervision, she presented with a severe episode of hematemesis at the 12th day of hospitalization due to rupture of esophagus.

Interventions

The massive hemorrhage was managed conservatively from Gastroenterologists with endoscopic esophageal stent insertion. After 14 days of hospitalization at ICU, she was hospitalized for 35 days at High Risk Pregnancy Unit of our Department. During the pregnancy, she was under close Obstetric and Psychiatric supervision. At 33th week of pregnancy, she was admitted again to High Risk Pregnancy Unit due to fetal growth restriction. She delivered by cesarean section a 1755g female neonate at 34+1 weeks of pregnancy.

Results

According to current literature, only 11 cases of Boerhaave syndrome during pregnancy have been published. The syndrome is reported as a complication to hyperemesis gravidarum in most cases, although our case had a psychogenic background. The gestational age varies and it can occur during all the trimesters of pregnancy, commonly during 1st trimester.

Conclusions

Boerhaave syndrome is very rare situation among young pregnant women. Only accurate diagnosis and immediate intervention can prevent death or serious illness and allow a favorable outcome for both the pregnant woman and the embryo.

Prenatal medicine and early pregnancy

A rare case of abdominally placed, non-communicating tubal pregnancy with unicornuate uterus; laparoscopic diagnosis and treatment

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Context
Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty

Objective
To report a very rare case of ectopic pregnancy, occurred in abdominally placed Fallopian tube in a patient with unicornuate uterus.

Methods
Case Report.

Patient
We aim to report a 32-year-old patient with epilepsy, right renal agenesis and left pelvic kidney, presented with abdominal pain and high β-hCG serum levels. The patient was suspected for ectopic pregnancy, diagnosed and treated with laparoscopic surgery. Intervention: In ultrasound examination, which was insufficient for identifying the location of ectopic pregnancy, free fluid was seen in pelvis. Severity of abdominal pain, total blood count and serum β-hCG levels were followed in hospitalized patient for suspicion of ectopic pregnancy. Diagnostic laparoscopy was performed. Unicornuate uterus with a normal left Fallopian tube and ovary was observed. On the contralateral site, in kidney location, right ovary and Fallopian tube were seen adherent to abdominal wall. Tubal ectopic pregnancy was seen in that noncommunicating right tube and salpingectomy was performed.

Main outcome measures
Emphasizing laparoscopic early diagnosis and treatment of a pregnancy of unknown location, highlighting and identifying a very rare embryological Mullerian pathology.

Results
A successful laparoscopic diagnosis and treatment of a very rare ectopic pregnancy in an embryologically incompletely migrated Fallopian tube.

Conclusion
The female reproductive tract structures (Fallopian tube, uterus, cervix, upper vagina) were formed as a result of complete migration and fusion of bilateral Mullerian ducts. In a variety of complications of Mullerian duct anomalies, ectopic pregnancy is an important one due to its morbidity and mortality. Laparoscopy may be a favorable approach for early diagnosis and treatment of an ectopic pregnancy when location can not be identified with repetitive ultrasonographic examination.

Prenatal medicine and early pregnancy

Endothelial dysfunction during pregnancy: prediction of child morbidity

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Objective

To study the influence of endothelial dysfunction, during the first trimester of pregnancy, on the health of neonates and infants by using cytometric studies of desquamated endothelial cells in the peripheral blood.

Material and methods

The study included 163 pregnant women with single fetuses. Endothelial dysfunction was assessed in mothers in their first trimester, on the basis of cytometric studies of desquamated endothelial cells in the peripheral blood. Physical health of patients (i.e. mothers) and their newborns was assessed. The contingent was divided into 3 groups. The first group was of 74 women where in the first trimester of pregnancy mean diameter of DEC of peripheral blood was more than 40 microns. 45 patients had a mean diameter of 30-40 microns, which formed the second group. 44 patients that had diameter less than 30 microns entered the third group.

Results

In patients with endothelial dysfunction detected in 1st trimester of pregnancy there was reduction in average diameter of desquamated endothelial cells. The children of these mothers more frequently encountered disorders of the Central nervous system and higher frequency of psychomotor developmental disorders. There was also a significant increase incidence of infections, inflammatory diseases and iron deficiency anemia in these kids. In group with mild degree of endothelial dysfunction in the first trimester – in 42.2% and in the third group – in 63.6% kids (after full term birth). Visceral dysfunction was diagnosed in 5,4% of children of the first group, 13.3% of children of second, and 27.3% of children in group with mothers having average to heavy degree of endotheliopathy. Frequency of hypoxic encephalopathy was 5.4% - in the first group, 13.3% - in the second group, and 31.8% - in the third group.

Endothelial dysfunction in patients with early 1st trimester pregnancy causes formation of an impaired utero-fetal relationship, which reflects in the formation of organ and systems in the fetus and leads to disorders in neonates and children of early pediatric age group.

Conclusion

Endothelial dysfunction is of huge importance and is consistent in defining somatic health of a newborn child. The cytometric analysis of endotheliocytes of peripheral blood of patients in their first trimester of pregnancy can be used as an informative test in early diagnosis of an increase in incidence of neonatal and early pediatric diseases.

Prenatal medicine and early pregnancy

Endothelial system of mother and fetus during the first trimester of pregnancy

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Endothelial dysfunction underlies many diseases associated with vascular lesions systems playing a primary role in development thrombosis, vascular remodeling and neoangiogenesis. Full-fledged implantation and establishment of adequate blood flow in the fetoplacental complex determine the successful development of pregnancy. Role study endothelial dysfunction in the development of pathology pregnancy, its effects on the processes of angiogenesis in chorion and placenta allows new effective methods for early diagnosis gravidar pathology.

Aim

to study the endothelial system in women with undeveloped pregnancy and their fetuses.

Materials and methods

The study included 180 first trimester pregnant women. The main group was composed of 90 women, whom a 7-10 week miscarriage was diagnosed followed by an instrumental abortion. The control group included 90 somatic healthy pregnant women, who chose to interrupt their pregnancy by an instrumental abortion. To characterize the endothelium system, we determined the number of desquamated endothelial cells together with cytometric evaluation of cell diameter, perimeter, area, shape, and polarization. Following the instrumental abortion, morphology of the fetal chorion was studied in women of both groups. Light microscopy was used to assess the fetal blood vessels and their differentiation. By means of computed cytomorphometry we determined the primary vessel wall thickness, lumen diameter and its area, as well as the Kernogan index.

Results

The cytometric analysis of desquamated endotheliocytes in pregnant women and that of fetal chorion blood vessels showed identical morphological changes in the endothelial systems of all examined women with pathological pregnancy. In the course of the study received significant differences in cytomorphometric indicators of the endothelial system of a pregnant woman and chorion of the fetus between the studied groups. A statistically significant increase almost 2 times the average number of desquamated endotheliocytes in pregnant women with non-developing pregnancy compared to control group. We used the method of qualitative and quantitative assessment of desquamated endotheliocytes, aimed at improving the accuracy of measurements, objectification of the obtained results.

Conclusion

The endothelial dysfunction found in the first trimester pregnant women is accompanied with changes in the endothelium of the fetal chorion, which can lead to pregnancy failure.

Prenatal medicine and early pregnancy

Is there any relationship between mutation in CPS1 gene and pregnancy loss?

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Background

Carbamoyl phosphate synthetase 1 (CPS1) is a liver-specific enzyme with the lowest enzymatic rate, which determines the overall rate of the other reactions in the pathway that converts ammonia to carbamoyl phosphate in the first step of the urea cycle. Carbamoyl phosphate synthetase 1 deficiency (CPS1D), which usually presents as lethal hyperammonemia, is a rare autosomal recessive hereditary disease.

Case

We report a case of a two-day-old female neonate with lethal hyperammonemia. The newborn infant was presented with hyperammonemia (34.7 µg/ml; reference range 1.1–1.9). In Plasma amino acid analysis, there was a significant elevated levels of alanine (3,004 µmol/L; reference range, 236–410 µmol/L), glutamine (2,256 µmol/L; reference range, 20–107 µmol/L), asparagine (126 µmol/L; reference range, 30–69 µmol/L), glutamic acid (356 µmol/L; reference range, 14–192 µmol/L), aspartic acid (123 µmol/L; reference range, 0–24 µmol/L), and lysine (342 µmol/L; reference range, 114–269 µmol/L). We cannot diagnose the urea cycle disorder (UCD) CPS1D properly only based on the quantity of biochemical intermediary metabolites to exclude other UCDs with similar symptoms. Following next generation sequencing determined one homozygous mutation in CPS1 gene and also this mutation was determined in her parents. The identified mutation was c.2758G > C; p.Asp920His, in the 23 exon of CPS1. This novel homozygous mutation had not been reported previously.

Conclusion

We applied whole exome sequencing successfully to diagnose the patient with CPS1D in a clinical setting. This result supports the clinical applicability of whole exome sequencing for cost-effective molecular diagnosis of UCDs.

Prenatal medicine and early pregnancy

The importance of recurrent pregnancy losses and anti-thyroid antibodies

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Abstract

When considered in definitive terms, although there is no clear consensus, recurrent pregnancy loss is a case of pregnancy loss under 3 and above 20 weeks or under 500 grams. According to another definition; two or more unsuccessful clinical pregnancies, three consecutive pregnancies (not necessarily intrauterine) losses revealed with ultrasonography or histopathological examination. Its incidence is 0.4-1%. When we consider it etiologically, the most commonly known cause is immunological factors; however, endocrine causes also cover a rate of 20%. In our case, the purpose was to emphasize the importance of elevated thyroid dysfunction levels, especially Anti-tg and Anti-tpo values in recurrent pregnancy losses.

The case

A 24-year-old female patient who had living baby through G4A3P1Y1 normal spontaneous vaginal way presented to our clinic because of recurrent miscarriages, all of which were 7-week. The patient, who had goiter as a systemic disease, and who was followed-up without drugs, did not have previous surgeries. In the pelvic examination of the patient, external genital organs were natural, collum multipar and adnexes were monitored free. In transvaginal ultrasonography, in uterus normal sonography, it was evaluated that endometrium was trilaminate, and bilateral ovaries were natural. Further examinations and imaging were applied. In genetic evaluation, the karyotype analysis of the patient and his husband was reported as normal. No pathologies were detected in the hysterosalpingography and spouse spermiogram of the patient. In the thrombophilia panel of the patient, MTHFR was reported as heterozygous mutant. The laboratory results of the patient were reported as antinuclear antibody was negative, lupus anticoagulant was negative, TSH:2.2 mu/l, free T4:1.9 ng/dl. There were no anomalies in the full blood, biochemical and hormonal parameters. Anti-thyroid peroxidase antibody: 146.3 u/ml, and Anti thyroglobulin: 216 u/ml were found to be elevated. The thyroid ultrasonography of the patient was carried out, and it was determined that the gland contours were smooth, echogenicity pattern was homogeneous, echogenicity severity was normal, and no lesions were detected forming boundaries and echo difference in the gland. The calibration of cervical vascular structures, and gray-scale lumen echo were reported as normal, and no lymph nodes were detected in cervical pathological dimension. The patient was evaluated in a multidisciplinary manner. The endocrinology clinic treated the patient for hypothyroidism in appropriate dose and duration. No pathological values were detected in the follow-up thyroid function tests and autoantibodies. The patient became pregnant six months after her last abortus. During the pregnancy, TSH, free T4 levels, and patient values were followed at 3-4 week intervals. The follow-up of the patient, who has reached the due date in pregnancy, is continuing.

Result

Endocrinological reasons should be evaluated in patients who have recurrent pregnancy losses. The relations of subclinical hypothyroidism with abortus must be investigated. The antithyroid antibodies being positive can also be considered as a predisposition to thyroid function disorder. In a metaanalysis, it was reported that the risk of miscarriage increased in women with Anti-tpo and Anti-tg positivity. In fact, they found that this increased the risk of miscarriage. There are studies reporting that the risk increases as a result of positive TGK and Anti TPO in euthyroid women. Thyroid disorders must also be kept in mind in case there are female infertility and failure of *in vitro* fertilization. The presence of thyroid autoantibodies is an independent risk factor in recurrent miscarriages. This situation is also a warning. The transition to obvious hypothyroidism must be avoided; it is a risk factor for obstetric complications. Attention must be paid in hypertension/preeclampsia, premature delivery, placenta rupture, low birth-weight, perinatal morbidity, cesarean risk, fetal and perinatal mortality, postpartum hemorrhage, and neurophysiological and cognitive impairment. The TSH and free T4 levels can be evaluated in the patient follow-ups. In addition, detailed information should be given to the couples with a history of recurrent miscarriage about preimplantation genetic diagnosis.

Prenatal medicine and early pregnancy

Long-term results of the different approach for management extra-uterine pregnancy

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Context
The purpose was to study the long-term results of the different approach for management extra-uterine pregnancy.

Objective. Methods
Retrospective analysis of 615 histories of patients with ectopic pregnancy has been performed, which were divided into 3 groups, depending on the type of treatment.

Patient
The first group consisted of patients, who were treated with laparotomy access (215 patient). The second group included patients with exacerbated ectopic pregnancy, who were operated by laparoscopic access (200 patient), the third group (200 patient) comprised patient, who were treated with methotrexate in a dose of 75-100 mg intramuscularly. In the structure of treatment methods there are significant changes from 2007 to 2017. Using ultrasound, the diagnosis of erly ectopic pregnancy was established by a transabdominal sensor in 40.4% of women, and by transvaginal sensor - in 74.1% of women.

Main outcome measure
The risk factors for developing ectopic pregnancy were following: early sexual life (OR = 4.36; 95% CI: (1.50-12.69); p <0.05), use of intrauterine contraception (OR = 6.9, 95% CI: (2.07-22.00), p <0.05), abortions and inflammatory diseases of genital organs (OR = 2.13; 95% CI: (0.63 -7.16); (p <0.05), pediatric infections (OR = 6.81; 95% CI: (2.05-22.65); p <0.05).

Results
Metrosalpingography showed that the patency of the fallopian tubes was significantly better in patient with methotrexate than after surgical treatment. Laparotomy was applied with the removal of the motor tube, infertility of tubal peritoneal genesis developed in 60 % of cases. The best result was shown by patients treated with methotrexate. The percentage of pregnancy in the natural way was almost 2 times highe, compared with surgical intervention. The use of methotrexate before surgery in patients with progressive ectopic pregnancy with high levels ofβ-HCG (> 1500 IU / L) and a fetal egg of more than 3.5 cm, followed by the conservative removal of a fertilized egg by laparoscopic access, helps to maintain the patency of fallopian tubes in 50% of cases. Patients in the third group receiving methotrexate noted a later onset of the next menstrual period (40.78 ± 2.13), which grew by 29.2% (p <0.05) compared with group I, and by group II by 33, 9% (p <0.05).

Conclusions
Patients with progressive ectopic pregnancy, with its accurate diagnosis, should be offered conservative medical treatment that will preserve the reproductive function of women in the future.

Prenatal medicine and early pregnancy

Results of cytokine research of pregnant women with the risk of premature birth

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Context

The physiological course of pregnancy is accompanied by a certain restructuring of the immune system, which ensures the mother's body's tolerance to fetal egg antigens and gestation. At present, it has become obvious that the protection of the fetus from the damaging maternal immune response is based on a complex mechanism and that communication between different steps in the cascade of events is carried out by cytokines [Musakhodzhayeva D. A. 2010].

Introduction

The aim of the study was to study the content of Pro-inflammatory and anti-inflammatory cytokines in pregnant women at risk of preterm birth (PR) Materials and methods. 42 women in the third trimester of gestation were examined. with the risk of premature birth. The cytokine status of IL - 1β, IL - 2, IL - 4, IL - 6, IL-8, IL - 10, and TNF-α in peripheral blood serum was determined by ELISA.

Results

The systemic cytokine status was studied in pregnant women at risk of preterm birth (PR). An imbalance of cytokines was found, characterized by an increase in the content of Pro-inflammatory cytokines and a decrease in anti-inflammatory interleukins, indicating an increased inflammatory response of the body in the Genesis of PR.

Conclusion

The study of cytokine balance is significant for assessing the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus. Excessive stimulation of the systemic humoral immune response as a result of increased activity of peripheral Pro-inflammatory cytokines and low secretion of anti-inflammatory cytokines are one of the fundamental mechanisms underlying the development of PR.In the last decade, active scientific research has been conducted to study the role of cytokines in the development of preterm birth (PR). At the same time the study of the immune system in pathological pregnancy may contribute to the pathogenetic substantiation of rational ways of ante - and intrapartum fetal protection and the prevention of complications in robotack way, we obtained the results of the study allow to assert that the study of cytokine balance is important to assess the orientation of the immune response, and pregnancy outcome for mother and fetus.

Prenatal medicine and early pregnancy

Assessment of perceived psychological stress in low risk pregnant who attend prenatal control

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Context
Pregnancy is a complex process that significantly impacts a women's life. Social influences, biological and psychological changes, are determining variables in maternal well-being. The adaptation to those changes, the appearance of morbid state and the expectations with the reproductive outcome, can lead to fear, stress and anxiety. Perceived psychological stress (PPS) is a common mental health problem that deserves adequate assessment in pregnant women. There are not enough studies on the implications of stress and other psychosocial factors in low-risk pregnant women in Latin American and Colombian populations.

Objective
Determine the frequency of PPS and identify associated factors in low-risk pregnancies.

Methods
A cross-sectional study that is part of the GESTACION research project. Anonymous and voluntary participation, approved by the ethics committee of the Santa Cruz of Bocagrande clinic, Cartagena, Colombia. Epi info 7.2 was used. Quantitative variables are presented in means and standard deviation, qualitative ones in absolute values and percentages. PPS was identified as a score above the mean obtained with Perceived Psychological Stress Questionnaire (PPS-10). Unadjusted bivariate logistic regression of the PPS (dependent variables) with sociodemographic characteristics and obstetric history (independent variables) was performed. $p<0.05$.

Patients
Pregnant women residing in Cartagena, the Colombian Caribbean, who attended prenatal control.

Interventions
Form of sociodemographic characteristics, obstetric history and perceived psychological stress questionnaire of 10 items (PPS-10)

Main outcome measures
PPS in pregnancy

Results
683 pregnant women were studied. Age 28,3±6,3; years studied 12,5±2,7; nutritional status (adjusted Rosso-Mardones): overweight 17.7%, obesity 33.0%. More than 60% never/almost never faced their things or solved their problems. PSS 51,2% was found. Factors associated with greater PSS: economic problems OR:2,9 [IC95%:2,0-4,3], infusions to sleep OR:2,7[IC95%:1,2-6,1], anxiety 2,0[IC95%:1,3-2,9], partner problems OR:1,9[IC95%:1,0-3,4], fatigue OR:1,7[IC95%:1,2-2,4], soda drinks OR: 1,3[IC95%:1,0-1,8]. Factors associated with less PSS: employed OR:0,5[IC95%0,3-0,7] and professional OR:0,5[IC95%:0,3-0,7].

Conclusion
PPS was present in half of the low-risk pregnant population. Many psychosocial factors were significantly associated.

Endometriosis and adenomyosis

A modern alternative for the management of clinical symptoms of adenomyosis

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Background

Adenomyosis is an important clinical problem in gynecology and healthcare economics. There are wide differences in the prevalence of adenomyosis. Among the Caucasian women is a high incidence of the clinical symptoms of adenomyosis, which adversely affects on the woman's QOL. Taking into consideration the pathogenesis of adenomyosis and specifics of its treatment, our attention has been focused on the mechanisms of contraceptive action of an etonogestrel subcutaneous implant-Implanon, which enables its potential use for the treatment of adenomyosis. Therefore, the aim of our study become to investigate the effects of etonogestrel on the uterus and clinical symptoms of adenomyosis.

Methods

For our cohort, prospective, open-label clinical trial,21 women(average age 25-45±3.9)with symptomatic adenomyosis were selected. We evaluated the intensity of non-cyclic pelvic pain and dysmenorrhea-using a daily NRS scale, QOL-using the EHP-30 questionnaire, intensity of menstrual bleeding-based on WHO patterns and change of uterine volume-using a GE Voluson 730Pro ultrasound machine-at baseline and 3,6,9,12,18 and 24 month follow-up. We defined the levels of Hb, serum CA125 and FSH, LH and E2 with the same intensity.

Results

During the 12-24 months of the study, the NRS score significantly decreased from 8.01±1.09 pre-implantation rate to 2.72±0.41 and to 1.81±0.13. Regular menstruation, amenorrhea, prolonged bleeding and increased frequency of bleeding were reported with the following incidence: 43%,29%,25% and 3% respectively. The QOL has improved significantly. The mean uterine volume decreased to 186.2±5.3cm3 after 12 and to 137.04±3.7cm3 within 24 months. Increased Hb levels were observed up to 120.04±2.56g/L and to 129.04±2.45g/L. Serum CA125 levels decreased to 42.11±8.14 and to 33.59±7.63. Serum hormone levels did not change significantly.

Conclusions

The results of our study detected the potential positive outcomes of an etonogestrel subcutaneous implant in women diagnosed with symptomatic adenomyosis. For which we can suppose that subcutaneous etonogestrel implant has the potential to become an alternative to surgical intervention and can be used for prolonged treatment of symptomatic adenomyosis with less pronounced adverse events and vividly positive pharmaco-economic effects. However, it should be noted that further long-term clinical trials and detailed analysis of the obtained results are needed, that may change the current approaches to clinical management of adenomyosis.

Endometriosis and adenomyosis

Pretreatment with dienogest in women with endometriosis undergoing *in vitro*-fertilization after a previous failed cycle

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Context

It is generally assumed that the major causes of *in vitro* fertilization (IVF) failure in women with endometriosis are diminished ovarian reserve, impaired endometrial receptivity and low quality of embryos. The use of prolonged courses of hormone therapy may improve the outcome of IVF in patients with endometriosis.

Objective

To evaluate the use of dienogest (DNG) before IVF in women with endometriosis.

Methods

This was a retrospective analysis of a prospective collected database involving 126 women aged 21–39 years who failed a previous IVF cycle and all subsequent embryo transfers. Patients had diagnosis of endometriosis at transvaginal ultrasonography or magnetic resonance imaging. Inclusion criteria for the study were age ≤ 40 years; basal FSH < 14.0 IU/L and antimullerian hormone (AMH) blood level ≥0.5 g/mL. Patients who had previous surgery for endometriosis were excluded from the study. Patients either directly underwent IVF without receiving hormonal treatment or received a three-month treatment with DNG (2 mg daily; Visanne, Bayer Pharma, Germany) before IVF.

Results

151 patients were included in the study, 88 underwent IVF without previous hormonal treatment and 63 received pretreatment with DNG. Age, average duration of infertility, antral follicle count, basal serum FSH, AMH and presence of endometriomas did not differ between the two groups at baseline. The implantation rate and clinical pregnancy rate were significantly higher in the DNG-treated group (39.7% and 33.3%) as compared with the non-treated group (23.8% and 18.2%; p=0.037 and p=0.033, respectively). The largest diameter and volume of endometriomas significantly decreased after pretreatment with DNG (-0.7 ± 0.8 cm and -3.1 ± 7.7 cm3, p<0.001 and p<0.001, respectively). A subgroup analysis demonstrated that the use of DNG increased significantly the number of oocytes retrieved (6.1 ± 2.8 versus 5.3 ± 2.2, p=0.039), of 2 pronuclear (2PN) embryos (2.9 ± 1.6 versus 2.2 ± 1.8, p=0.015) and of blastocysts (2.4 ± 1.6 versus 2.0 ± 1.4, p=0.049) obtained in patients with endometriomas with diameter ≥ 4 cm.

Conclusions

In women with endometriosis, outcomes of IVF can be improved by pretreatment with DNG. DNG improves the implantation rate in patients with endometriosis and number of 2PN embryos and blastocysts in patients with large endometriomas.

Endometriosis and adenomyosis

Impact of metabolic and antioxidant treatment on free circulating DNA and it methylation profile in patient with endometriosis

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Endometriosis is a chronic inflammatory condition where endometrial cells migrate outside the uterus, mainly to pelvis tissues and organs. Genetics and epigenetics also play a role in the development of endometriosis. Recent studies suggest a role of oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and antioxidants, which may be involved in the pathophysiology of endometriosis causing a general inflammatory response in the peritoneal cavity. ROS are intermediaries produced by normal oxygen metabolism and are inflammatory via oxidative stress and its role in the development of endometriosis (Scutiero et al 2017).

Xiao Yan Zhong et al (2009) reported that circulating free DNA (cfDNA) was significantly higher in the endometriosis group than in control group. The author concluded that circulating cfDNA may be a potential biomarker for endometriosis. In our study, we selected a group of 32 women (16 without a history of endometriosis and 16 with a history of endometriosis) to evaluate by PCR their serum cell free DNA. The endometriosis group contained on average 4 times more cfDNA than the control group. (1051ng/ml versus 251,034 ng/ml). The cfDNA of 5 women from each of the two groups was submitted to a Whole Genomic Study (WGS) and for each of the genes, the methylation status analysed.

This showed in 158 isolated genes, 92 hypermethylated and 66 hypomethylated with a panel of 87 of genes implicated in the endometriosis development: 58 hypermethylated and 29 hypomethylated.

After this first analysis all patients were treated with antioxidant and metabolic formulation (Proxeed Women) for 3 months. Thereafter the cfDNA was measured by real time quantitative PCR. The data showed a decrease of free circulating DNA in all patients and mainly in a significant pattern of the severe endometriosis cases with an change of methylation profile mainly in 15 specific genes.

This preliminary data need to be continued for large cohort of patient to confirm how the anti oxidants impact the apoptosis and the inflammatory pathway in positive way to reduce the cfDNA in peripheral blood and how the methylation status, or expression level of a group of genes is dysregulated in endometriosis patients. The study showed that these changes in endometriosis could be counteracted by treatment with an antioxidant formulation containing L-carnitine and acetyl-L-carnitine probably by reducing oxidative stress which is high in this condition.

Endometriosis and adenomyosis

Endometriosis: role of epigenetic regulation of estrogen and progesterone receptors

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Context
Endometriosis is now recognized as a estrogen-dependent and inflammatory disorder disease. Estrogen together with estrogen receptor including estrogen alpha(ESR1) and estrogen receptor beta(ESR2) and progesterone receptor(PgR) play a crucial role in the development of endometriosis. There were several studies concentrating on the methylation effect on the expression of ESR and PgR. The evidence of the effect of DNA methylation on the expression of ESR and PgR was limited not only in the number of samples but also in the different subtypes of endometriosis, which need more studies to explore the methylation level of ESR and PgR in different sites and different patients.

Objective
The evaluation of methylation level of PGR, ESR1 and ESR2 in fresh tissue of deep infiltrating endometriosis (DIE).

Methods
Tissue collected from women with DIE treated with surgery in the hospital Negar, Verone, Italy and put in a preservative liquid then stored at 4°C until DNA extraction. DNA extraction was performed by All prep DNA/RNA protein Minikit(QIAGEN). The DNA quality was checked and the methylation profile was performed by enzymatic cuts with EpyTect Methyl II DNA restriction Kit and PCR Assay and evaluated by specific algorithms.

Patient(s)
Individuals who suggested to have DIE with non-invasive tests and finally confirmed by surgery were selected. 15 patients were finally included in the research totally.

Intervention(s)
-

Main outcome measure(s)
The methylation level of selected sites of PGR, ESR1 and ESR2.

Result(s)
On the 8/15 samples observed, the median value of the level of methylation in the promoter of ESR1 was 12% which is in low methylation level with a broad range from 4% to 97%. On islet 1 of the promoter of ESR2, all the samples have an amplification in wild type. No methylation was observed in 3/15 samples and the median value of 15/15 samples was 5% which is very low level of methylation with a range of 0-100%. On islet 2 of the promoter of ESR2, no amplification was observed in 3/15 samples. In the rest 12/15 samples, one was no methylation while the median of the 11/15 samples was 3% which is a very low level of methylation with a range of 0-100%. In the islet 1 of the promoter of PgR, 8/15 were methylated with a median value of 55% which is a intermediate level of methylation with a range of 7%-99.5%. And about the islet 2, the median value of methylation was 23% which is a low level with a range of 1%-100%.

Conclusions
Methylation of DNA influence deeper in PgR than ERs expression. ERs and PgRs show some changes in the sequence observed of their promoters. Further investigations are needed to analyze the sequence in those samples with no amplification and the demographics of the patients.

Endometriosis and adenomyosis

The differences of eutopic and ectopic endometrium of women with endometriomas and normal endometrium

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Context
The eutopic endometrium in adult women with endometriosis is different in many ways from that of healthy subjects both in the proliferative and secretory phases, with heterogeneous responses (Brosens et al., 2013).

Objective
The aim of study was to compare the levels of platelet-derived growth factor receptor (PDGFR) and stage-specific embryonic antigen 1 (CD15) in the eutopic and ectopic endometrium of patients with endometriomas and endometrium of women without endometriosis.

Methods
Evaluation of the results was carried out using a point scale: 0 is the absence of membrane staining or the presence of weak staining of less than 10% of cells, 1 - weak membrane staining of more than 10% of cells; 2 - moderate membrane staining of more than 10% of cells or strong membrane staining of less than 30% of cells, 3 - strong complete membrane staining of more than 30% of cells.

Patients
94 patients of reproductive age were divided into 2 groups: I (main) group included 70 patients with endometriomas, II group comprised 24 patients with infertility without endometriosis.

Interventions
Diagnostic laparoscopy and hysteroscopy with endometrial sampling for immunohistochemistry study were performed in group II. Patients of I group undergone endoscopic removal of the endometriotic cyst, hysteroscopy and subsequent immunohistochemistry investigation.

Results
In I group, an increase in CD15 expression in ectopic endometrium in comparison with eutopic was observed in both glands (35 (32; 37), 8 (8; 9), p=0.002) and in the stroma (16 (15; 22), 1 (0.8; 1.3), p=0.003), as well as similar changes in PDGFR as in glands (38 (38; 41), 9 (8; 10), p=0.002), and in the stroma 18 (17; 19), 1.1 (0.8; 1.4), p=0.001). There was an increase in CD15 (8 (8; 9), 8 (6.5; 8), p=0.006) and PDGFR (9 (8; 10), 8 (7.5; 9), p=0.001) in the glands of the eutopic endometrium in comparison with normal.

Conclusion
the higher levels of expression of CD15 and PDGFR in ectopic endometrium in women confirm the theory of the role of stem cells in the pathogenesis of endometriosis and differences of eutopic, ectopic and normal endometrium.

Endometriosis and adenomyosis

Can hormonal treatment with desogestrel in women with pelvic endometriosis achieve menopause?

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Objectives

Evaluate the possibility of hormonal treatment with desogestrel to long term control symptomatology and recurrence of pelvic endometriosis.

Material

Eighty one women diagnosed with pelvic endometriosis who underwent hormonal treatment by desogestrel 75mcg tabletes per day were accompanied at the Women's Health Reference Center (Pérola Byington Hospital), São Paulo, Brazil. At the end of 12 months of treatment, 66 patients (81,5%) remained, those who had a good clinical response to pelvic pain (dysmenorrhea and/or chronic pelvic pain) through visual analog pain scale (VAS pain) in mm and abnormal uterine bleeding, and were tracked for up to 108 consecutive months. Serum estradiol dosages were performed in pg/mL and CA-125 in U/mL at times 0, 12, 24, 36, 48, 60, 72, 84, 96 and 108 months of treatment.

Results

Symptoms of dysmenorrhea and/or chronic pelvic pain according to the VAS of 66 patients at month 0 were 9.1 mm, and after 12 months decreased to 2.7mm and remained stable until 108 months of treatment. Regarding abnormal uterine bleeding, 26 patients that at the beginning of treatment had some kind of alteration, at the end of 12 months all of them had a favorable bleeding pattern (amenorrhea, infrequent bleeding or monthly bleeding). Serum estradiol dosages at times 0, 12 and 84 months were 83.4, 70.2 and 70.0 pg/mL, respectively. Serum CA-125 dosages at times 0, 12 and 84 months were 45.1, 19.6, and 18.5U/mL, respectively. Concerning menopause, 17 patients (25,8%) had laboratory confirmation during treatment, at the average age of 50.2 years old.

Conclusion

The good clinical response in the use of desogestrel in women with pelvic endometriosis with improved symptomatology may extend long term, and achieve the menopausal transition. Although, other studies must be directed to prove safety in the long term use of this medication.

Endometriosis and adenomyosis

Different proteomics analysis indicates metformin as a novel therapy to ameliorate endometrial receptivity of infertile women with minimal/mild endometriosis

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Context
Endometriosis reduces female fecundity, most of endometriosis-associated infertility women are diagnosed with minimal/mild endometriosis. The decreased endometrial receptivity should be responsible for the pathogenesis. Metformin inhibited the growth of ectopic lesions, while the effect of metformin on eutopic endometrium of minimal/mild endometriosis has not been reported.

Objective
This study aims to identify whether metformin can ameliorate eutopic endometrial receptivity in infertile women with minimal/mild endometriosis.

Methods
Secretory phase endometria (10 pairs) were simultaneously collected by hysteroscopic curettage and Endometrial Suction Curette (Pipelle) after 2 months metformin therapy (1000mg/d) (5 cases) or non-received controls (5 cases). Protein expressions profile of eutopic endometrial tissues were analyzed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) based proteomics with data-independent acquisition (DIA) workflow. Validation studies using parallel reaction monitoring (PRM) were performed for up-regulated biomarkers associated with endometrial receptivity. Paired t-test was carried out to identify differential protein expression and bioinformatic analysis was performed, including GO, KEGG, PPI.

Patients
Total of 10 infertile women with minimal/mild endometriosis diagnosed by laparoscope were enrolled into the study.
Interventions: This is a controlled trial to compare protein expression in eutopic endometria of minimal/mild endometriosis patients after 2 months treatment of metformin (1000mg/d).

Main outcome measures
Differentially protein expressions profile of eutopic endometrial tissues after metformin treatment.

Results
A total of 20 endometrial samples were analyzed. Compared to baseline, 149 differentially expressed proteins were detected in the endometria after metformin therapy. Insulin-like growth factor-binding protein 7 (IGFBP-7), α-antitrypsin (AAT), apolipoprotein D (ApoD), Rho GDP-dissociation inhibitor 1 (Rho-GDI), brain form glycogen phosphorylase (PYGB) and Cathepsin B (CTSB) that associated with endometrial receptivity had up-regulated after metformin therapy ($P<0.05$); while the expressions of those protein had no significant change in controls. Expression of IGFBP-7 and ApoD had been validated by PRM.

Conclusions
Our study revealed that metformin, an insulin sensitizer, may ameliorate endometrial receptivity of eutopic endometrium of minimal/mild endometriosis in molecular aspects, that could be used as potentially novel therapy to improve the fecundity of infertile women with minimal/mild endometriosis.

Endometriosis and adenomyosis

In endometriosis the cell-to-cell contacts during epithelial-mesenchymal transition are intact

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Context

Epithelial-mesenchymal transition (EMT) is an important process of cell remodelling during development and organogenesis, but also in diseases like cancer and fibrosis. It is defined by loss of the epithelial and gain of a mesenchymal phenotype, where cells often acquire migratory and invasive capabilities. Many reports also claimed EMT in the pathogenesis of endometriosis and described loss of cell-to-cell contacts, especially of claudin-3, -4 and -7.

Objective

In this study we analysed the cell-to-cell contacts, especially claudins, in patients without and with endometriosis in order to validate the suggested loss of the epithelial phenotype in endometriosis.

Methods

We performed an immunohistochemical study with antibodies against claudin-2, -3, -7 and -11 on tissue sections of patients with and without endometriosis and the three endometriotic entities, ovarian and pelvic endometriosis and deep infiltrating endometriosis (DIE). Quantification was done with the HSCORE.

Main Outcome

Only claudin-11 showed an impaired localization from the apicolateral junctions to a basal or basolateral localization in ovarian and peritoneal endometriosis, and DIE.

Results

We found a preferential localization of claudin-2/-3 in the glandular cells in the endometrium with and without endometriosis. Quantification of claudin-2/-3 showed no differences in eutopic endometrium of controls compared to cases with endometriosis and are also highly similarly in the ectopic compared to the eutopic endometrium.

Furthermore, we identified claudin-7 primarily at the basolateral junctions of the glandular epithelial cells in eutopic and ectopic endometrium in nearly all glands and cysts. Quantification showed a slight increase of claudin-7 in peritoneal and DIE compared to eutopic endometrium. In contrast, claudin-11 was localized mainly in the apicolateral junctions in nearly all glandular epithelial cells of the eutopic endometrium. Interestingly, we observed a deregulation of claudin-11 localization to a basal or basolateral localization in ovarian ($P<0.001$), peritoneal ($P<0.01$), and DIE ($P<0.05$) and a moderately decreased abundance in ovarian endometriosis.

Conclusions

There was no loss of cell-to-cell contacts in the endometrial and endometriotic epithelial cells, only some changes in the localization of claudin-11 in ectopic endometrium. Thus, we suggest that only a partial EMT, without loss of the epithelial phenotype, is involved in the pathogenesis of endometriosis.

Endometriosis and adenomyosis

Characterization of M1 and M2 macrophages in ovarian endometriomas in early and advanced stages of endometriosis: do they contribute to the progression of the disease?

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Context

Endometriosis is an estrogen-dependent disease. Macrophages are broadly classified into pro-inflammatory M1 macrophages, and M2 macrophages, which have selective anti-inflammatory and pro-fibrotic activities and are able to induce immunotolerance and angiogenesis.

Objective

We aimed to evaluate M1 and M2 macrophages in tissue samples from ovarian endometriomas in women affected by endometriosis at different stages of the disease.

Methods

For each patient, we collected a biological sample of the cyst (ovarian endometriomas for cases and ovarian functional cyst for controls) during laparoscopy. The tissue was weighed, reduced to small pieces, extensively washed in PBS to remove debris and aggregates of red blood cells. The tissue fragments were digested, filtered, washed and centrifuged in PBS to remove excess enzymes. Cell viability was tested by Trypan blue and was considered satisfactory above 95%. The obtained cells were incubated with the following monoclonal antibodies in a 1: 100 dilution and characterized by flow cytometry, as follows: M1 macrophages were identified by CD14 conjugated with fluorescein isothiocyanate (FITC), CD68 conjugated with Biotin, CD197 (CCR7/REA546) conjugated with phycoerythrin-Violet 770 (PE-Vio770), CD80 conjugated with allopicocyanin (APC); M2 macrophages were identified by CD14 conjugated with FITC, CD68 conjugated with Biotin, CD163 conjugated with PE-Vio770, CD206 conjugated with APC.

Patient(s)

Women affected by endometriosis at different stages of the disease, with at least one ovarian endometrioma (cases); women affected by a single ovarian functional cyst persistent for more than 6 months (controls).

Intervention(s)

Observational analysis of tissue samples.

Main outcome measure(s)

Quantification of CD14+CD68+CD197+CD80+ M1 and CD14+CD68+CD163+CD206+ M2 macrophages.

Result(s)

The number of both M1 and M2 macrophages was significantly higher in endometriosis group than controls, regardless of stage ($p < .0001$ for each stage versus controls). Moreover, our data analysis shows a trend in progressive decrease of M1 macrophages from stage I to stage IV; on the contrary, M2 macrophages show a specular trend compared to M1 macrophages, with a progressive increase from stage I to stage IV.

Conclusions

M1 macrophages may contribute to the pro-inflammatory microenvironment in the early stages of the disease, whereas M2 macrophages may account for the pro-fibrotic activity of the advanced stages.

Endometriosis and adenomyosis

A connection between adenomyosis and subfertility

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Context
Adenomyosis is uterine structural pathology characterized by the endometrial invasion surrounded by benign smooth muscle hyperplasia within myometrium. Uneven thickening of the endometrium-myometrium junctional zone (JZ) and depth of the invasion of adenomyosis may lead to subfertility. There is a need to establish criteria of JZ pathology and related impact of adenomyosis on fertility.

Objective
To determine the pregnancy outcomes in patients with thickening of JZ.

Methods
We measured JZ thickness (the thickest part, JZmax) and depth of invasion of adenomyosis into myometrium. The ratio between the maximum and minimum thickness of the JZ (the coefficient of symmetry of the JZ) was determined.

Patients
102 women (aged 18-39) with adenomyosis who were planning to conceive in 12 months. Factors possibly contributing to infertility, such as, submucosal fibroids, tubal infertility, primary ovarian failure or male infertility, were excluded. The patients were divided in two groups: Group 1(n=58) - nulliparous patients with no history of previous intrauterine interventions and Group 2(n=44) - multipara women with any of those.

Interventions
MR imaging of the uterus was performed during luteal phase of a menstrual cycle.

Main outcome measures
Mean JZmax values in pregnant patients were 8.5±4.0mm and 12.2±3.0mm in infertile patients in Group 1, and 11.7±2.7mm and 13.0±4.4mm, respectively, in Group 2 ($p<0,05$). The coefficients of symmetry of the JZ in pregnant patients were 5.5±3.9mm and 8.9±2.8mm in infertile patients, in Group1, and 7.4±3.4mm and 8.0±3.8mm, respectively, in Group 2 ($p<0,05$).

Results
The JZ max threshold for subfertility outcomes was estimated as: 9.1mm in Group1 and 9.4 mm in Group 2. The infertility rate was 56,9% in Group 1 and 61,4% in Group 2 ($p<0,05$). There were 13,8% (Group 1) and 22,7% (Group 2) cases of threatened miscarriage, which were successfully managed to birth. Normal pregnancies were in 22,4% of patients in Group 1 and in 9,1% of patients in Group 2 ($p<0,05$). There was no significant difference in miscarriages in both groups (6,9% vs. 6,8%, Group 1 vs. Group 2, respectively, $p>0,05$). The correlation between the depth of invasion of adenomyosis to the myometrium and pregnancy outcome estimated as $Pr=0.004$ ($p<0,05$) in Group 1 and as $Pr=0.39$ ($p>0,05$) in Group 2.

Conclusion
The increasing JZ max thickness and depth of invasion of adenomyosis into myometrium impact pregnancy outcomes due to impaired embryo implantation.

Endometriosis and adenomyosis

Management of women with ovarian endometrioma and infertility: surgery or IVF?

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Context

Ovarian endometrioma is the typical manifestation of endometriosis. It affects up to 17-44% of women with endometriosis and is often associated with infertility and pelvic pain. Growing evidence indicates that endometrioma itself, especially ones of big size, and previous ovarian surgery can reduce ovarian reserve (OR). It becomes a bigger problem in infertile women of advanced reproductive age. Nowadays controversy exists about first-choice treatment – surgery or IVF.

Objective

To summarize published evidence-based literature data to evaluate benefits and risks of surgical treatment and IVF management in women with ovarian endometrioma and infertility.

Methods

We performed electronic search using PubMed, MEDLINE, Cochrane Library for identification of systematic reviews, meta-analysis and clinical guidelines of professional societies and associations published in last 5 years with following key-words: AMH, ovarian reserve, endometriosis, endometrioma, surgery, IVF.

Results

We identified 12 systematic reviews and meta-analysis, RCOG, NICE, CNGOF/HAS guidelines and recommendations of ESGE, ESHRE, WES and ETIC working groups.

OR is reduced in women with endometriomas compared with other benign cysts and healthy ovaries due to oxidative stress, free iron toxity, proteolytic enzymes action and long-lasting mechanical stretching that can cause follicular loss. However, authors do not recommend cystectomy to improve ART outcomes, as they find no difference between surgery and conservative management in pregnancy and live birth rates. If surgery is needed to access follicles in normal ovarian tissue or for symptomatic women who plan to conceive, authors suggest sclerotherapy or suture for hemostasis during cystectomy of large cysts. In late reproductive age OR is low per se. According to international guidelines, clinicians are recommended to counsel women before treatment about all outlined risks of reduced ovarian function.

Conclusion

We found no evidence in favor of surgical treatment of endometriomas prior to ART if the only indication is subfertility. According to evidence-based literature data, IVF may be considered first line. Meanwhile, the solution should be based on individual conditions such as age, cyst's size and follicular accessibility, OR levels, previous surgeries and symptoms.

Endometriosis and adenomyosis

Catamenial pneumothorax

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Introduction

Pneumothorax may occur primarily and secondarily. Primary causes are usually sporadic and familial history has rarely been reported. Secondary causes occur most commonly secondary to COPD. Pneumothorax caused by endometriosis is a rare condition. In our case, pneumothorax developed 6 times simultaneously with the menstrual cycle and there was a complaint of infertility. We aimed to present the case having improvement with hormonal treatment.

Case

A 36-year-old patient who had two normal spontaneous vaginal delivery had regular menstrual cycles, and she had complaints of dysmenorrhea and infertility. The patient had a history of pneumothorax operation with simultaneous menstrual cycles 6 times in the last 3 years. The edematous reaction was reported on the pathology results obtained from the lung operations of the patient, and infiltrative lesions were observed according to subsequently obtained radiological imaging of the lung on the anterior side of the right lower lobe from which samples could not be obtained during operation. Lesions with brown-red dot areas were evaluated as suspicious areas for endometriosis in the intraoperative examination.

In the pelvic examination of the patient, the collum was evaluated as multiparous and adnexa as free vaginal relaxed. Transvaginal ultrasonographic examination showed normal uterine sonography and no endometrial pathology. There was a cystic formation in the left ovary which was compatible with 3 cm endometrioma. No pathology was observed in the right adnexal area. In the laboratory examinations, CA 125 was reported as 12.52 U/Ml in the normal range.

Thorax High-Resolution Tomographic examination showed nodules of 2 mm-5 mm in diameter in the lateral and lower lobe superior segments of the right lung, and band formation was observed.

The patient was evaluated as catamenial pneumothorax considering the intraoperative evaluation and her history, and 3 mg drospirenone and 0.03 mg ethinylestradiol treatment were applied regularly for 6 months, the patient did not have pneumothorax attacks during the following 1 year period.

Conclusion

Endometriosis and non-endometrial catamenial conditions, which are rare causes of pneumothorax, should be considered and multidisciplinary opinions should be taken. It should be kept in mind that hormonal treatment may be beneficial.

Endometriosis and adenomyosis

Evaluation of the effectiveness of treatment of endometriosis with oxytocin receptor inhibitor on the basis of experimental model of the disease

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Context
Endometriosis (E) is a chronic, progressive, estrogen-dependent disease. Currently, there is no single approach and universal method of treatment that would guarantee complete cure and absence of recurrence of the disease. It is known that endometrial cells possess receptors for oxytocin, which is able to trigger synthesis of prostaglandins E2 and F2α. Induction of aromatase activity by prostaglandin PGE2 in endometrioid cells is responsible for increased expression of CYP19A gene, increase in intracellular cAMP levels and synthesis of 17β-estradiol.

Objective
To evaluate efficacy of oxytocin receptor inhibitor (IOR) Atoziban on a model of surgically induced genital endometriosis in Wistar rats.

Methods-Intervention (s)
The study included 24 sexually mature female Wistar rats aged 10 to 12 weeks, weighing 220 to 290 g. All the experimental animals underwent 3 consecutive surgical interventions. The first stage was formation of a model of endometriosis via laparotomy. After 2 weeks from the beginning of the experiment, formation of foci was evaluated by laparoscopic access with subsequent randomization into two groups. After randomization, 12 rats of the main group were initiated daily intraperitoneal administration of IOR at a dosage of 0.35 mg/kg / day. The second, control, group (12 rats) received injections of saline solution. The third stage was the end of the experiment after 21±3 days from the beginning of IOR administration or saline solution injections and measurement of the size of endometrioid heterotopies after dissection of experimental animals.

Result(s)
43 implants were formed in 24 rats. At the beginning of treatment, the average surface areas of endometrioid implants were comparable in both groups - 18.3±2.5 mm^2 in the main group and 17.5±3.5 mm^2 in the control group. In the main group (22 heterotopies), complete resorption of implants was detected in 27.3% of cases, in 68.2% there was a significant decrease in the area of heterotopies by 62.4±11.2%. In the control group, there was an increase in the size of endometriosis foci in 95.2% of cases by 29±7.2%. The average area of endometrioid implants in the main group after treatment was significantly lower than in the control group.

Conclusions
Obtained results demonstrate high effectiveness of IOR in the treatment of surgically-induced endometriosis in rats. This therapeutic approach can be considered to be a promising direction in the treatment of this disease.

PolyCystic Ovary Syndrome

Is the histomorphology of PCOS endometrium different from one of regular cycle women?

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Abstract Background

The infertility problem of women with PCOS is not restricted to anovulation process. In fact, the embryo implantation on the endometrium is other factor that may contribute for low rate of pregnancy after ovulation induction. However, there is little information on the endometrial tissue of this patients under adequate dose of progesterone.

Objective

The aim of this study was to evaluate the endometrium of PCOS patients using natural progesterone.

Materials and Methods

Voluntary women with PCOS (n=20) and women with regular menstrual cycle (control group, n=20) have included in this study. Endometriual biopsies were scheduled for both groups. The PCOS patients with amenorrhea (>90 days) was performed a endometrial biopsy. After that those patients received a 10-day natural progesterone treatment (400mg/day) intravaginally. After the 14th day of bleeding, the treatment was repeated then the biopsies were performed between the 20th and the 24th day of the bleeding. Women with regular menstrual cycle received two cycles of natural progesterone intravaginally for 10 days (400mg/day) starting on the 14th day of the menstrual cycle. On the second menstrual cycle, the biopsies were performed between the 20th and the 24th day. The endometrial samples were processed for histological route and evaluated on the light microscopy for histomorphological evaluation. ANOVA test was run for multiple comparisons.

Results

In the PCOS group, after the treatment with progesterone, the endometrium showed the same features described in the first stage of the menstrual cycle, although the superficial and glandular epithelia were more thickened (n=9) compared to control group ($p<0.023$). The superficial epithelium of PCOS is more uniform, with less number of leukocyte and apoptosis figures compared to control group ($p<0.021$). The samples of PCOS collected on proliferative phase presented large endometrial superficial epithelial thickness compared to PCOS women who received natural progesterone ($p<0.012$). In addition, non-PCOS women had a significant smaller superficial epithelial thickness than PCOS women ($p<0.004$).

Conclusions

Our data suggest that the use of micronized progesterone 400 mg may be not sufficient to restore the normal morphology of the endometrium.

PolyCystic Ovary Syndrome

Activated micronutrients in support to the one carbon cycle modulate circulating homocysteine in PCOS women

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Parthenogen

Context
Fasting blood homocysteine (Hcy), an index of oxidative damage, is increased in PCOS and is involved in several of its co-morbidities including cardiovascular disease and infertility. Recent findings suggest a primary role of oxidative imbalance in the generation of insulin resistance rendering Hcy a possible therapeutic target in PCOS. Metformin, which may help in preventing cardiovascular diseases in PCOS, generates a counter effective increase of homocysteine posing a clinical dilemma. Corrective interventions based on administration of supra-physiologic doses of folic acid work to a low extent. Indeed, folic acid may support only one of three possible Hcy recycling pathways.

Objective
To test the efficacy of a new approach in modulating circulating Hcy in PCOS, i.e. the administration of multiple micronutrients, where possible in activated form downstream to possible genetic weaknesses, supporting all the pathways for Hcy removal.

Methods
This was a prospective, randomized, parallel group, open label, controlled versus no treatment clinical study.

Patients
PCOS women aged > 18, free from systemic diseases and from drug treatments were randomized with a 2:1 ratio for treatment (n = 22) or no treatment (n = 10).

Intervention
The active intervention group received an oral supplement containing physiologic doses of L-cystine, betaine, zinc, niacin, riboflavin, pyridoxin, methylfolate and methylcobalamin during 3 months (Impryl, Parthenogen, Switzerland). The control group received no treatment.

Main outcome measures
Patients were tested at baseline and at the end of follow-up for fasting blood homocysteine, AMH, testosterone, SHBGs and the resulting FTI.

Results
At baseline, mean fasting blood Hcy inversely correlated with SHBG and was above the normal limit of 12 µMol/L. AMH was also increased. Testosterone, SHBG and FTI were within the normal limit. The treatment significantly reduced of Hcy, that did not change in the control group, independently of the starting value with some reduction in all the treated patients (100% response). The treatment also caused an increase of AMH and a decrease of SHBGs only in the subgroup with a normal homocysteine at baseline.

Conclusions
Mean fasting blood Hcy was increased PCOS ladies and inversely correlated to the SHBGs. Physiologic amounts of activated micronutrients in support to the carbon cycle reduced it virtually in all exposed patients. Whether this is of clinical benefit remains to be established.

PolyCystic Ovary Syndrome

Do artificial neural networks predict metformin therapy responsiveness in PCOS patients?

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Context

Metformin in PCOS patients decreases androgen levels and improves metabolic and ovulatory functions. Nevertheless, its extensive use is contained by the highly variable response rate.

Objective

Aim of this study is to identify reliable predictors of response to Metformin therapy, using the artificial neural networks (ANN)

Methods

Cohort study.

Patients

113 PCOS consecutive patients (ESHRE/ASRM 2003 Rotterdam criteria), treated with Metformin 1500 mg/day, by the Gynecological Endocrinology outpatient clinic of the Reproductive Medicine Unit San Paolo Hospital-Milan.

Interventions

At inclusion and every 6 months during treatment patients underwent to a complete clinical, endocrine and metabolic assessment and TV-ultrasonographic evaluation. Semantic connectivity maps were obtained through Auto-CM system, a fourth generation ANN, in order to compare patients' baseline clinical and lab parameters to the treatment outputs.

Main outcome measures

Therapy outcomes were BMI reduction ($\geq 1 kg/m^2$) in the overweight/obese subpopulation and free-androgen-index (FAI) decrease ($\geq 1\%$) in hyperandrogenemic patients.

Results

Metformin treatment resulted successful. At 6 months 54 out of 82 (65,85%) obese patients showed BMI reduction and 45 out of 68 (66,17%) hyperandrogenemic women showed FAI decrease. Respectively at 12 months 88,37% and 60,41%. The semantic connectivity maps showed a clear polarization for BMI reduction since the 6 months observation highlighting the role of raised FAI, oligomenorrhea and insulin resistance at baseline. Conversely the maps for FAI reduction showed a clear polarization and better accuracy only at 12 months observation and demonstrated the relationship between the same variables plus hirsutism score, BMI and hypertriglyceridemia and the treatment response. Classifying each patient as responder vs non responder, according to the shortest path connecting her discretized variables in the map, we obtained an overall accuracy ranging from 81% to 87%.

Conclusions

Through the Artificial Neural Networks we highlighted the baseline features of a good Metformin responder, so becoming able to predict, with a reasonable accuracy, the treatment response of every patient in our population. Our results certainly open a new promising research way in the fields of PCOS treatment and reproductive medicine.

PolyCystic Ovary Syndrome

The effects of metformin, pioglitazone and empagliflozin on metabolic control, hormonal imbalance, weight loss and ovulations in obese patients with polycystic ovary syndrome and impaired glucose tolerance

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Context
Many studies confirmed the role of metformin in PCOS treatment and several reported positive effects of thiazolidinediones and SGLT2 inhibitors on metabolic parametars in these patients.

Objective
The aim of this study was to compare the effects of metformin, pioglitazone and empagliflozin on metabolic control, hormonal imbalance, weight loss and ovulations in obese patients with PCOS and impaired glucose tolerance.

Methods
BMI, waist circumference, HOMA index, leptin/adiponectin, FSH/LH, androstendione, testosterone, DHEAS, triglycerides, cholesterol, HDL, LDL and presense of ovulation were tested at the admission and 12 months after therapy.

Patients
146 patients (mean age 25±2,6) with PCOS and impaired glucose tolerance were divided in 3 groups based on medication they were treated with.

Results
Empagliflozin was superior to metformin ($p>0.05$) in weight loss, and metformin was superior to pioglitazone ($p<0.05$). Empagliflozin was superior to metformin ($p<0.01$) and pioglitazone ($p<0.01$) in reducing waist circumferences. Pioglitazone ($p<0.01$) and empagliflozin ($p<0.01$) were superior to metformin in lowering HOMA index. Empagliflozin was superior to metformin in raising SHBG ($p<0.01$) but not superior to pioglitazone. Empagliflozin was superior to metformin in lowering L/A ($p<0.05$) but not superior to pioglitazone. Metformin was superior to pioglitazone ($p<0.001$) and empagliflozin ($p<0.001$) in lowering LH/FSH. Metformin was superior to pioglitazone ($p<0.001$) and empagliflozin ($p<0.001$) in lowering testosterone. Metformin ($p<0.001$) and Empagliflozin ($p<0.01$) were superior to pioglitazone in reducing androstendione. There was not difference between groups in reducing DHEAS. Pioglitazone ($p<0.001$) and Empagliflozin ($p<0.001$) were superior to metformin in reducing triglygerides. Empagliflozin ($p<0.001$) was superior to metformin in lowering cholesterol levels but not superior to pioglitazone. Empagliflozin ($p<0.001$) and pioglitazone ($p<0.001$) were superior to metformin in raising HDL. Empagliflozin ($p<0.001$) and pioglitazone ($p<0.001$) were superior to metformin in lowering LDL. There was no difference between groups in ovulatory menstrual cycles.

Conclusions
Metformin, Pioglitazone and Empagliflozin were equally efficient in regulating menstrual cycles in patients with PCOS. Pioglitazone and Empagliflozine were superior to metformin in metabolic control while metformin was superior in resolving hyperandrogenism. Pioglitazone and Empagliflozin can be a second therapy of choice in patients with PCOS.

PolyCystic Ovary Syndrome

Carotid intima-media thickness in polycystic ovary syndrome and its association with hormone and lipid profiles

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Context

Polycystic ovary syndrome (PCOS) has been associated with an increased risk of metabolic disturbances and cardiovascular disease. Intima-media thickness of the common carotid artery (CIMT) represents a valid surrogate marker of early systemic atherosclerosis.

Objective

This study aimed to investigate if CIMT is increased in PCOS patients compared to healthy controls and if there is an association with hormone and metabolic profiles.

Methods

Patients: In this prospective cross-sectional study, 41 PCOS patients were consecutively recruited and compared to 43 age-matched healthy controls of similar body mass index (BMI) and frequency of smokers. Interventions: Past medical history, anthropometrical measurements and hormonal, lipidemic and glycemic parameters were obtained in all subjects. B-mode ultrasound enabled CIMT measurement at the far wall of the left and right common carotid artery. Outcome Measures: Statistical analyses were performed using unpaired two-tailed t-test, $\chi 2$-test and multiple linear regression analysis in order to identify independent factors that predict CIMT. Two-sided P-values<0.05 were considered statistically significant.

Results

Patients with PCOS showed significantly increased CIMT values compared to healthy controls (0.49±0.04mm vs. 0.37±0.04mm respectively, P<0.001). They featured a generally increased cardiovascular risk profile, with higher prevalence of visceral obesity, dyslipidemia, hyperandrogenemia (P<0.001) and parental history of metabolic disorders (P=0.001). Correlation analysis showed a positive association between CIMT and the adverse metabolic risk profile. The diagnosis of PCOS was the strongest predictor of CIMT (β=0.836, P<0.001, R2=0.70), even after multiple adjustments for BMI, age and smoking status (β=0.797, P<0.001, R2=0.73). A model among oligomenorrhoic patients revealed a relationship between CIMT and the suspected duration of disease (β=0.373, P=0.021, R2=0.14).

CONCLUSIONS

Pcos patients are likely to feature signs of premature systemic atherosclerosis at a young age. Early exposure to adverse cardiovascular risk factors in the framework of this disorder may possibly have long-term consequences on the vascular system. An early vessel screening might thus already be beneficial in these patients at a younger age.

PolyCystic Ovary Syndrome

Mitochondrial dysfunction and systemic inflammation in adolescent girls with polycystic ovary syndrome in regarg to excessive BMI and insulin resistance

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Context
Mitochondrial dysfunction (MD) and systemic inflammation play an essential role in the pathogenesis of PCOS

Objective
To evaluate the impact of MD and SI in PCOS pathogenesis during adolescence with regard to body weight and insulin resistance (IR).

Methods
Clinical and laboratory examination; CRP, Leptin, cytokines (TNF-α, IL-6, IL-10, IL-18, MIF) malondialdehyde (MDA), % of highly polarized mononuclear cells (MNC), apoptotic factor and it's ligand (sFas/sFasL).

Patients
The study included 90 girls from 15 to 17 years old with PCOS with classic phenotype A, divided into 4 groups according to the presence of excessive BMI and IR; 30 healthy girls with regular menses in control group.

Results
Inflammatory activation in IR obese PCOS patients vs controls was evidenced by higher levels of proinflammatory cytokines IL-18 (134,7±118,9 vs. 65,1±72,6 pg/ml,≤ 0,05), IL -6 (0,62 (0,24-1,20) vs. 0,39 (0,05-0,86),=0,03) and MIF (2,61±3,11 vs. 1,84±2,51,≤ 0,05). On the contrary PCOS lean non IR group was characterized with higher level of anti-inflammatory IL-10 compared to controls (0,9±0,6 vs. 0,6±0,3 pg/ml,=0,025).
Mitochondria respiration persists at a higher level in the lean non IR PCOS group against controls (%of highly polarized MNC (57,3±12,91 vs. 51,2±8,7, p<,05)). The highest content of MNCs with highly polarized mitochondria produce a bigger amount of ROS in this group, but due to adaptive increased antioxidant defense the Oxidative stress (OS) is controlled. And increased LPO we see only in combination of excessive weight and MD, due to the lack of antioxidant defense.
Multifactorial analysis confirmed excessive weight is an independent factor of OS activation (MDA, p<0,0001), MD (% MNC with highly polarized mitochondria,=0,0286) and systemic inflammation (CRP,=0,0028; Leptin,=0,0007). Metabolic disorders – factor of systemic inflammation (Leptin,=0,0083; IL- 18,=0,0137) and apoptosis activation (sFas/sFasL,=0,0163). Excessive weight and MD combination leads to a double activation of OS (MDA,=0,0273) and systemic inflammation (MIF,=0,0228).

Conclusions
Lean girls with PCOS demonstrate the protective mechanism of decrease in OS mediated by the activation of antioxidant defense, reduction of lipid oxidation and systemic inflammation. Excessive weight and metabolic disorders in adolescents with PCOS are the most significant factors in reducing the capacity of antioxidant systems, activation of OS, MD and systemic inflammation.

PolyCystic Ovary Syndrome

Complex assessment of the effect of glycosaminoglycans on the system of haemostasis in patients with polycystic ovary syndrome

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Context
Polycystic ovary syndrome (PCOS) is one of the most common diseases among women of reproductive age. It has a significant impact on various body systems. Endothelial dysfunction plays an important role in the pathogenesis of polycystic ovary syndrome. It increases the risk of cardiometabolic complications. The appointment of drugs containing glycosaminoglycans in its composition allows to prevent the development of cardiovascular complications due to angioprotective and profibrinolytic effects.

Objective
To evaluate the effect of glycosaminoglycans with high affinity to the endothelium on the system of hemostasis in patients with polycystic ovary syndrome.

Methods
Patients with PCOS were divided into 2 groups, according to the body mass index: patients with normal body weight (n=30) and patients with obesity (n=30) for the purpose of comparative assessment of the hemostatic system and analysis of the effectiveness of vasoprotective drug.

Patient(s)
The study included 60 patients diagnosed with polycystic ovary syndrome. The control group consisted of 30 healthy patients with normal body weight.

Intervention(s)
During the study, all patients underwents a comprehensive assessment of the main indicators of the hemostasis system.

Main outcome measure(s)
The results of the study indicate a significant impact of endothelial dysfunction in polycystic ovary syndrome on the hemostasis system regardless of body weight.

Result(s)
The use of glycosaminoglycans has proven its feasibility and effectiveness as an angioprotective agent in the presence of PCOS. In patients with metabolic disorders, glycosaminoglycans have a more significant therapeutic effect, which is confirmed by the pronounced dynamics of platelet count, level of fibrinogen, thrombin time, level of homocysteine.

Conclusions
Taking into account the presence of endothelial dysfunction in patients with polycystic ovary syndrome, the use of glycosaminoglycans helps to reduce the risk of cardiovascular complications, which allows to improve the results of pregravid preparation, as well as to increase the level of favorable perinatal outcomes in this cohort of patients.

PolyCystic Ovary Syndrome

Markers of inflammation in PCOS: plasmatic free light chains of immunoglobulins and correlation with testosterone levels

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Context

PCOS, as systemic disease, is accompanied by different indexes of inflammation. Free light k and λ chains of immunoglobulins (FLCs), produced by plasmacells, are released in slight excess for the immune requests, with still poorly defined physiological role but surely they represent a marker of inflammation. No data in literature are available on their levels in PCOS.

Objective

To evaluate levels of FLCs and correlate them with hyperandrogenism.

Methods

FLCs were assayed by turbidimetric method, hormonal parameters by ECLIA Patients. We have studied a group of PCOS patients (n= 16, age range 18-37 ys, mean±SEM BMI 24.1±0.9 Kg/m^2), compared with age- and BMI-matched controls (n=24, age range 20-31 ys, mean±SEM BMI 20.8± 0.4 Kg/m^2), with assay of k and λ FLCs.

Interventions

Morning blood sample collection for FLCs, hormonal and metabolic parameters.

Main outcome measure(s)

FLCs levels and ratio k/λ, correlation with HOMA-ir index and androgen levels

Result(s)

PCOs exhibited higher levels vs controls: (mean ± SEM λ:10.0±0.85 mg/L vs 8.41±0.45 mg/L; k: 12.45 ± 0.72 mg/L vs 6.41±0.34 mg/L; k/λ 1.31 ±0.07 vs 0.78 ± 0,04). A significant direct correlation was observed between λ-FLCs and testosterone levels, no correlation was indeed found with HOMA-IR index.

Conclusions

These data confirm an inflammatory condition, not only related to insulin-resistance; FLCs could be a useful marker and also another step forward to understand the physiopathology of such complex syndrome.

PolyCystic Ovary Syndrome

Genetic and hormonal approach in metformin effectiveness prediction in PCOS patients

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Context

Since insulin resistance (IR) was observed to play a role in PCOS pathogenesis metformin (Mf) has been used in its treatment. The effectiveness for menstrual cycle restoration (MCR) is about 60% and hardly depends on IR existence. Therapy effectiveness prediction is important to reveal nonresponders.

Objective

To evaluate molecular-genetic and hormonal markers of Mf therapy effectiveness in patients with PCOS.

Methods

Transvaginal sonography, AMH, LH, FSH, total testosterone (TT), androstendione levels evaluation, dual-energy X-ray absorptiometry and oral glucose tolerance test were provided. SNPs were genotyped by PCR or NGS for 46 loci, associated with IR, impaired folliculogenesis and androgen biosynthesis. Statistic analysis was carried out with SPSS Statistics 21.

Patients

143 women (mean age – 26.4±4,6 years, mean BMI – 23/8±4/8 kg/m^2) with PCOS (Rotterdam criteria, 2003).

Intervention

Mf 1500 mg per day during 6 month. All patients were divided into 2 groups: the 1st – patient with MCR (53.1%), the 2nd – with lack of therapy effect (36.3%). Women with partial effect (10.6%) were excluded from the study.

Main outcome and measure

MCR (5-6 menstrual bleeding per 6 months), hormonal and genetic markers of Mf effectiveness.

Results

Both groups were comparable by age, BMI, phenotype and IR frequency. Mean AMH, TT levels and index A/G were lower in group 1 ($p<0.05$). ROC-analysis in prediction of MCR after Mf treatment showed that the area under the curve (AUC) for AMH model was 0.705 (cut-off level - 13.3 ng/ml), AUC for TT – 0.622 (cut-off level – 1.81 ng/ml), AUC for index A/G 0.698 (cut-off level – 0.9). Molecular-genetic analysis showed that C/C genotype in FSHR (rs2349415) was associated with 4.5-fold (p=0.0143) and Del/Del genotype in OCT1 (rs113569197) was associated with 7.5-fold (p=0.0167) higher frequency of MCR. C allele in SLCO1B1 (rs4149056, p=0.0222) and Del allele in ACE (rs4340, p=0.0408) were associated with the MCR. The most predictive model of MCR included serum AMH level and genotype of FSHR (rs2349415) (AUC=0.8, sensitivity 82.1%, specificity 54.5%, p=10-4). The probability of response for patients with AMH under 13.3 ng/ml and FSHR rs2349415 C/C was 100%, and for patients with AMH above 13.3 ng/ml and T-carrier – only 37.5%.

Conclusion

in each 2nd woman with PCOS prescribed with Mf therapy MC was restored. AMH level and genotype FSHR (rs2349415) could serve as useful tools that could make treatment more effective.

PolyCystic Ovary Syndrome

Does the ovarian stroma color Doppler have a good correlation with phenotype A-PCOS features?

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Abstract

Polycystic ovary syndrome (PCOS) is considered an endocrine and metabolic disorder with systemic, reproductive, psychological, cosmetic and oncological repercussions. According to Rotterdam criteria (2003), the diagnosis is based on the presence of two out of three characteristics: clinical and biochemical hyperandrogenism, chronic anovulation and polycystic ovaries on ultrasonography, excluding other causes of hyperandrogenism. Its pathophysiology is complex. Genetic factors, intrinsic abnormalities of ovarian steroidogenesis, hyperinsulinemia and hyperandrogenemia, with consequent anovulatory cycles and changes in ovarian follicular development are involved. It is postulated that in PCOS there is an increase in follicle size, confirmed by the anti-Müllerian hormone (AMH) dosage as well as the increase of androgens in the ovarian stroma. The ultrasound pattern of the ovaries in this syndrome is characterized by the presence of twelve or more follicles with a diameter between two and nine millimeters in both or at least one of the ovaries. Surveys that correlate ultrasonographic aspect with androgen production are scarce. Recent advances in two-dimensional (2D) and three-dimensional (3D) Doppler ultrasonography can be applied in the investigation of ovarian arteries.

Objective

The aim of this research is to evaluate the ultrasonographic characteristics and its correlation with the hormonal, metabolic and body composition profile in women with PCOS.

Methods-Patients

This is a cross-sectional prospective study and we analyzed 98 women (61 with PCOS and 37 controls) attended at the Gynecological Clinic Division of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Brazil. Intervention: The use of Color Doppler for evaluating the ovary and compare these results to Phenotype A PCOS features: Anamnesis and anthropometric data, sonographic characteristics of the ovary, serum hormone dosages (FSH, LH, estradiol, AMH, total and free testosterone, prolactin, 17-hydroxyprogesterone, TSH, T4L), biochemical glucose after 75g of dextrosol, insulin curve, total cholesterol and fractions, triglycerides) were studied. Subsequently, the statistical correlation of the data was performed, starting from the differences found between the groups.

Main outcome measure

Data of ovarian stroma color dopper.

Results

The different factors significantly associated with moderate or severe ovarian vascularization were estradiol > 43.5 [OR = 2.62 (95% CI 1.04-6.63), p = 0.033]; LH / FSH ratio > 2 [OR = 4.67 (95% CI 1.58-1.81), p = 0.004]; free testosterone > 36 [OR = 153.12 (95% CI 26.32-890.7), p <0.001]; total testosterone > 49 [OR = 23.62 (95% CI 6.67-83.58), p <0.001]; androstenedione > 1.0 [OR = 6.02 (95% CI 2.232-16.219), p <0.001]; fasting insulin > 25 [OR = 5.96 (95% CI 1.75-20.31), p = 0.002]; right ovary volume > 10 [OR = 14.8 (95% CI 4.7-46.00), p < 0.001; left ovary volume > 10 [OR = 5.00 (95% CI 1.83-14.82), p = 0.002]; more than 9 follicles > 0.5 cm [OR = 24.01 (IC95 % 7.21-83.86), p <0.001]; stromal area> 2.1 [OR = 2.93 (95% CI 1.15-7.48), p = 0.038].

Conclusion

The Color Doppler had good correlation with ovarian volume and testosterone blood concentration. Therefore, it may be used for evaluation the ovaries of PCOS patients

PolyCystic Ovary Syndrome

Differences in metabolic profile between phenotypes of polycystic ovary syndrome (PCOS)

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Context

The Rotterdam criteria for PCOS recognized four phenotypes, distinguished based on the presence of hyperandrogenism (HA), oligo- and/or anovulation (oligo) and polycystic ovaries (PCO) in ultrasound examination. According to the proposal of Dunaif and Diamanti- Kandarakis, depending on the state of insulin sensitivity there are two phenotypes of PCOS- reproductive and metabolic. Choosing the treatment option in PCOS the phenotype and metabolic abnormalities should be consider.

Objective

To evaluate the differences in metabolic profile in women with different phenotype of PCOS based on Rotterdam criteria and insulin resistance status.

Methods

One thousand one hundred women with PCOS, aged 17 to 40, were recruited. Firstly the participants were divided into four phenotypes- (A): oligo+ HA +PCO; (B): oligo+ HA; (C): HA+ PCO, (D): oligo+ PCO. Secondly, 2 subgroups were distinguished based on the state of insulin sensitivity defined by HOMA-IR, fasting insulin concentration and insulin concentration after oral glucose loading. Blood samples were collected between 3rd and 5th day of the menstrual cycle to evaluate serum hormone levels and quantification of metabolic parameters. Anthropometric measures were assessed in subjects from each group.

Results

In groups with HA worse metabolic profile was observed. There were statistically significant differences in total cholesterol and LDL level between subgroups A and D. The lowest triglycerides (TG) concentration was observed in patients without HA. Groups with HA were characterized by significantly higher body mass index (BMI). Patients with insulin resistance (IR) had significantly higher total cholesterol level, LDL, TG and fibrinogen concentration with lower HDL compared to thus with persistent insulin sensitivity. IR was moderately negatively correlated with total cholesterol level, LDL, TG and fibrinogen, while positively with HDL.

Conclusions

Patients with HA are characterized by higher BMI, worse lipid profile and therefore higher risk of future metabolic disorders. Co-occurrence of IR is accompanied by dyslipidemia and higher fibrinogen level. That's why in PCOS treatment without additional negative influence on lipid parameters, body mass and coagulation should be preferred, such as dydrogesterone in monotherapy or as a component of hormonal replacement therapy either oral contraceptive pills contain levonorgestrel with low-dose estradiol.

PolyCystic Ovary Syndrome

Glycative stress and sirtuin deregulation in the ovaries of DHEA-induced PCOS mice

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Context

In the last decade, the advanced glycation end products (AGEs) have been implicated in the pathogenesis of PCOS. Methylglyoxal (MG), a byproduct of glycolysis, is considered the most powerful AGE precursor. AGE accumulation is triggered by altered glucose metabolism, increased oxidative stress and deregulation of the MG detoxification enzymes, glyoxalase 1 (GLO1) and glyoxalase 2 (GLO2). MG-dependent glycative stress in mouse female gonad involved a SIRT1 functional network.

Objective

By using a PCOS mouse model induced by administration of dehydroepiandrosterone (DHEA), we investigated whether MG-dependent glycative stress contributes to ovarian PCOS phenotype and explored changes in the SIRT1 functional network regulating mitochondrial functions and cell survival.

Methods, Patient(s), Intervention(s)

CD1 female mice aged 21 days received 20 consecutive doses of DHEA (60 mg/kg). To monitor PCOS phenotype, we monitored estrous cyclicity by vaginal smears. Follicle counting was carried out after H&E-staining. To assess steroidogenesis, 17HSD4 expression was evaluated. Immunofluorescence analysis (IF) was employed to monitor TOMM20, a mitochondrial marker. Von Willebrand Factor and SMA were used for assessing vascularization. Bodipy was used for lipid droplets evaluation. Western blot analysis anti-SIRT1, SIRT3, SOD2, GLO1, GLO2, PGC1α, RAGE, MG-AGE, mt-TFA, 17HSD4, AMPK pAMPK1, LC3, p62 and GAPDH. After induction of ovulation, metaphase II oocytes were subjected to IF for evaluating mitochondrial potential by JC-1 staining, spindle and chromosomes configuration.

Main Outcome, Measure(s), Result(s)

Anovulation and reduced oocyte quality were observed in DHEA mice along
with increased vascularization, lipid droplets accumulation and altered steroidogenesis. We detected increased MG-AGE levels in association with increased expression of RAGEs (receptor for AGEs) and deregulation of the glyoxalasesystem, hallmarks of glycative stress. Then, DHEA mice exhibited enhanced ovarian expression of SIRT1 along with increased protein levels of SIRT3 and SOD2 and decreased PGC1α, mtTFAM and TOMM20. Finally, the presence of autophagy protein markers and increased AMPK activation suggested the involvement of SIRT1/AMPK axis in autophagy activation.

Conclusions

Present findings support the hypothesis that MG-dependent glycative stress underlies ovarian dysfunctions associated to PCOS and suggest that a SIRT1-dependent adaptive response is involved.

PolyCystic Ovary Syndrome

Beneficial effects of acyl-L-carnitines during oocyte IVM after mild oxidative stress

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Context

Reactive oxygen species (ROS) are implicated in nearly all aspects of human reproduction. When elevated intracellular ROS cause damage to lipids, proteins and nucleic acids, a condition known as oxidative stress (OS) is established. There is much evidence that oocyte developmental competence can be seriously hampered by OS arisen during physiological events including aging and ovarian dysfunctions such as PCOS (Polycystic ovarian syndrome). L-carnitines are natural compounds with free-radical scavenging activity. They play a pivotal role in mitochondrial oxidation of long-chain fatty acids and are essential for oocyte and early embryo development. Growing evidence suggests that L-carnitines exert beneficial effects on reproductive potential of PCOS patients.

Objective

In the present study we compared the effects of Propionyl-L-carnitine (PLC) and acetyl-L-Carnitine (ALC) plus L-Carnitine (LC) on oocyte *in vitro* maturation (IVM) after exposure to mild OS.

Methods, Patient(s), Intervention(s)

Ovarian GV (germinal vesicle) oocytes from CD1 mice were exposed 25 μM H2O2 for 30' prior to IVM in M16 medium supplemented with different PLC (0.2-2 mg/ml) or ALC (0.02-0.8 mg/ml) +LC (0.04-1.6 mg/ml) concentrations. After 16 hours, oocytes showing first polar body (MII) were subjected to spindle immunostaining and chromosome detection. MII configurations were classified as: i) Normal; ii) Slightly Aberrant: slight disorganisation with max 4 scattered chromosomes; iii) Aberrant: disorganised chromosome plate or decondensed chromatin. Spindle was classified as: i) Normal: bipolar focused normal spindle; ii) Slightly Aberrant: slight disorganisation or slight abnormal shape of the spindle; iii) Aberrant: disorganised or abnormal or absent spindle.

Main Outcome, Measure(s), Result(s)

At the end of IVM, 1mg/ml PLC was found to increase the percentage of oocytes showing first polar body in comparison to control and H2O2 groups. Mild OS induced a 50% reduction of oocytes showing normal and slightly aberrant spindle and chromosome configuration. PLC was able to prevent these effects. By contrast, ALC+LC supplementation did not significantly improve IVM rate and oocyte quality after OS.

Conclusions

Supplementation of medium with PLC during IVM improved oocyte ability to resume meiosis after mild OS. Further analysis will help us to understand the molecular mechanisms underlying PLC activity against mild OS, which alters ovarian physiology in conditions like PCOS.

PolyCystic Ovary Syndrome

The sonographic ovarian stroma cut-off as a hallmarker for phenotype A of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is considered an endocrine-metabolic disorder with systemic repercussions, whose diagnosis, according to the criteria of Rotterdam (2003), is based on the presence of two of the three characteristics: clinical or biochemical hyperandrogenism, chronic anovulation and polycystic ovaries (ultrasound with 12 or more follicles 2 to 9 mm or volume from 10 cm^3 in one or both ovaries), excluding other disorders with similar clinical presentation.

Objective

To evaluate the sonographic ovarian stroma of patients with PCOS and to correlate it with anthropometric, clinical, hormonal and metabolic profile data. Methos - patient: prospective cross-sectional study that analyzed 76 women, 39 of them with PCOS phenotype A (mean age 29 ± 6 years) and 37 included in the control group (mean age 34 ± 7 years), attended at the Gynecological Clinic Division, from the Hospital das Clínicas, Faculty of Medicine, University of São Paulo, Brazil, between 2016 and 2018.

Intervention

Anamnesis, physical examination, laboratorial and two-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound data were collected. Subsequently, statistical correlation of the data was performed, starting from the differences found between the groups.

Main outcome measure

The evaluation of sonographic ovarian stromal area and correlaction with clinical and laboratorial features of PCOS patients.

Results

The correlation data with 2.1 cm3 of stroma area present the characteristics with higher and lower frequency in the PCOS group in a crude and adjusted manner for the following parameters: androstenedione > 1.0 [OR = 6.07 (95% CI 2.24-16.42), p <0.001]; estradiol > 43.5 [OR = 4.16 (95% CI 1.59-10.85), p = 0.003]; LH / FSH ratio > 2 [OR = 11.93 (95% CI 3.13-45.42), p <0.001]; right ovarian volume > 10 [OR = 16.29 (95% CI 5.04-52.62), p <0.001], left ovarian volume > 10 [OR = 10.24 (95% CI 26.00-32.08), p <0.001]; moderate-marked ovarian vascularization [OR = 153.12 (95% CI 26.32-890.79), p <0.001]; DHEA-S > 1,580 [OR = 0.35 (95% CI 0.13-0.91), p = 0.026]; SHBG > 40 [OR = 0.10 (95% CI 0.033-0.29), p <0.001]; and Matsuda Index > 2.5 [OR = 0.21 (95% CI 0.07-0.63), p = 0.006].

Conclusions

Our results allowed to conclude that stroma area larger than 2.1cm3 may be an ultra-sonographic marker of ovaries from PCOS patients.

PolyCystic Ovary Syndrome

Effects of behavioral modification on psychological well-being in overweight women with polycystic ovary syndrome (PCOS) b: a randomized controlled trial

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Context
Lifestyle intervention is a first line treatment in PCOS. There is increasing evidence that women with PCOS have impaired psychological well-being. Little is known on how lifestyle changes affect well-being.

Objective
To evaluate the effects of behavioral intervention on psychological well-being in overweight women with PCOS.

Methods
Patients were randomized to structured Behavioral Intervention (Intervention) or Standard Advice (Control) on a 1:1 ratio for comparison at 4 months. All were evaluated at 12 months when the Control group also had received the intervention. Well-being was assessed using the Psychological General Well Being Index (PGWBI).

Patients
68 women fulfilling all three Rotterdam PCOS criteria, aged 18-40 years, with a BMI b %27 kg/m^2.

Interventions
The Intervention was a structured course, including weekly meetings, focusing on weight control, personal leadership, physical activity and diet. The Control group received standard advice.

Outcome Measures
Primarily we investigated the change to mean global PGWBI and its six dimensions at 4 and 12 months. Furthermore, the relationship between well-being and weight loss was studied.

Results
At baseline, 60% of all had a global PGWBI corresponding to severe distress and 40% to moderate distress. No-one was in the positive well-being category. There was no change in mean global PGWBI between baseline and 4 months within or between intervention groups. However, for the intervention group, the mean score improved in three dimensions at 4 months: anxiety (p=.035), general health (p=.012) and depressed mood (p=.033). The change in anxiety and general health tended to be significant between groups (both p=.06). There was no difference in mean global PGWBI or in any dimensions between baseline and 12 months. However, we found that women achieving b %5% weigh loss at 12 months (n=18) were less anxious at baseline compared to the ones who had not lost weight (p=.004). In addition, there was a larger proportion of women in the category of moderate distress compared to the category of severe distress who had managed to lose b %5% weight (p=.05).

Conclusions
Psychological well-being is exceptionally low in this population. Behavior modification can have a positive effect on some dimensions of well-being. Achieving weight loss is associated with higher well-being. This highlights the importance of assessing and addressing the psychological status prior to embarking on lifestyle change.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

NK cell activity in women with multiple reproductive losses

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Context
Pregnancy development on early stages is more susceptible to genetic and immunological factors. Despite the great interest of researchers in this problem, the role of immunological factors in the genesis of reproductive disorders remains not fully understood. One of the most pressing issues is the role of NK cells in the genesis of reproductive disorders.

Objective
Assessment of the functional activity of peripheral blood NK cells in women with multiple reproductive losses (recurrent miscarriage of early pregnancy and IVF failure).

Methods
In addition to the standard examination, each patient was evaluated for the subpopulation of lymphocytes, the activity of NK cells by the expression of CD107a, as well as by interaction with trophoblast cells of the JEG-3 line in the presence and absence of IL-2.

Patients
70 women with 2 or more loss of clinical pregnancy, which occurred in the natural cycle (up to 10 weeks); 41 women with 2 or more unsuccessful attempts at ART (IVF, IVF / ICSI, cryotransfer); 65 healthy fertile women with 1 or more healthy children, 50 women who did not have a history of pregnancy, without a burdened obstetric-gynecological history.

Results
In healthy fertile women, the number of cells expressing CD107a spontaneously was lower than in the IVF failure group ($p < 0.001$), but did not differ from the RM group. Moreover, in healthy women, after activation, their number increased most significantly (19.8 times), 11.5 times in the RM group, and only 4.3 times in the IVF failure group.
In fertile women, a decrease in the cytotoxic activity of NK cells against JEG-3 trophoblast cells from the proliferative to the secretory phase of the menstrual cycle was observed, and in the group of women with habitual miscarriage, an increase in cytotoxicity

Conclusion
The functional activity of NK cells, determined by the CD107a marker, as well as by the interaction with trophoblast cells of the JEG-3 line, is significantly different in patients with reproductive losses and the control group. Depending on the severity of reproductive disorders, the functional activity of NK cells changed: in the group with IVF failures, initially increased activity of NK cells was observed at rest, and in the RM group, after activation, the potential of NK cells was significantly reduced compared to fertile women.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

The use of intravenous immunoglobulins in women with multiple reproductive losses

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Context
Despite the large arsenal of modern treatment measures, the number of women with multiple reproductive losses does not decrease. In this category of patients, the use of standard examination and therapy protocols does not lead to positive results. Given the proven association of recurrent micarriage of early pregnancy and IVF failures with immunological disorders, various immunomodulatory therapies have been studied in these patients.

Objective
To evaluate the effectiveness of the use of intravenous immunoglobulins in women with multiple reproductive losses (recurrent miscarriage of early pregnancy, IVF failure) and changes in the activity of peripheral blood NK cells before pregnancy.

Methods
In addition to the standard examination, each patient was evaluated for the subpopulation of lymphocytes, the activity of NK cells by the expression of CD107a.

Patients
61 married couple with 2 or more losses of clinical pregnancy in the period up to 10 weeks, which occurred in the natural cycle; 41 married couples with 2 or more IVF failures; 27 healthy fertile women with 1 or more healthy children.

Interventions
When detecting violations of the functional activity of NK cells, intravenous immunoglobulins were used at a course dose of 10 gr twice at the pregravid stage - 1 time in 4 weeks under dynamic control of indicators of the number and activity of NK cells; after a positive analysis for hCG; again after 4-5 weeks

Results
In the group of RM in the vast majority of women, pregnancies were prolonged for more than 24 weeks. Pregnancy complications such as retrochorial hematoma and placental insufficiency were observed more often in those who did not receive immunotherapy. In group 2, significant differences in the frequency of biochemical pregnancy were obtained - 87.5% in those who received therapy versus 30% in those who did not.

Conclusions
In patients with reproductive losses and diagnosed immunological abnormalities, the use of intravenous immunoglobulins has an immunomodulating effect, reducing the number of NK cells, and a pronounced clinical effect, increasing the frequency of biochemical pregnancy in women with multiple implantation failures by 3 times, reducing the frequency of early gestational losses in women with habitual miscarriage 5 times.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Efficacy of treatment of treatening miscarriage during multiple pregnancy after ART with progesteron

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Context

Multiple pregnancy turns out to be a vital problem of modern obstetrics, as the need for ART is growing every year, followed by the frequency of multiple pregnancies. It is known that patients with induced multiple pregnancy are subject to more frequent miscarriage and obstetric complications. While the use of progesterone drugs for preventing the termination of a singleton pregnancy has shown its high efficiency (the B level of evidence), there is little evidence of the efficacy of progesterone drugs for the case of multiple pregnancy.

Objective

Examining the peculiarities of the multiple pregnancy process and the outcomes of the childbirth of ART patients who received the therapy of threatened abortion using progestogen.

Methods

There was a prospective cohort study involving 97 pregnant women after ART with the threat of miscarriage in the first trimester.

Patients

The group I included 58 patients received didrogesterone therapy. The group II included 39 pregnant women received micronized progesterone. The patients of 2 groups were comparable in age, the burden of obstetric and gynecological history, and the threat of pregnancy termination.

Interventions

The group I received didrogesterone therapy at a dose of 40 mg/day per os. The group II received micronized progesterone at a dose of 400 mg/day per vaginum. Symptoms of the threat of pregnancy termination stopped within 2 weeks in both groups. Both groups took progesterone drugs in a maintenance dose and a prolonged mode until the 26th week of gestation.

Main outcome measures and results

The treatment of threatening miscarriage in the first trimester was effective in 93.6% ($p>0.05$) of the cases. The permanent threat of pregnancy termination in the second trimester due to the diagnosis of cervical insufficiency was recorded for patients in both groups (41.3% and 55.2%, $p>0.05$). The group I patients experienced cervix shortening 2 times less often, which confirms its higher efficiency (26.1% and 55.2%, $p>0.05$). The frequency of the preterm birth for patients group I was 20% lower than for group II. (74% and 53%, $p>0.05$). Bacterial vaginosis was detected 4 times more often for patients taking the vaginal form of progesterone (62.1% and 17.2%, $p>0.05$).

Conclusions

The administration of dydrogesterone and micronized progesterone for the treatment of threatening multiple pregnancy miscarriage in the first trimester and further progesterone support up to 26 weeks of gestation are highly effective.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Pregnancy outcomes predicted by gycemic values in the oral glucose tolerance test

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Background

Gestational diabetes is the most common metabolic disorder during pregnancy and it is recognised to be associated with macrosomia and other complications like neonatal hypoglycaemia, maternal pre-eclampsia or eclampsia. Recently, gestational diabetes and pre-eclmpsia were clified as risck factors for maternal risk of cardiovascular diseases near the well know risk for glycemic and metabolic diorders later in the maternal life

Objectives

The aim of the present study was to assess the associations of plasma glucose values during the oral glucose tolerance test (OGTT) effectuated between 24-28 weeks of pregnancy with adverse outcomes in women with gestational diabetes and to identify predictors for these pregnancy outcomes.

Methodology

The present study included women with gestational diabetes and a control group and it is a retrospective analysis of a prospectively collected database from a clinic highly specialized in diabetic pregnancies. Diagnostic OGTT was performed at a gestational age of 27 weeks (mean) using the 75 g glucose test.

Results

In aproximately 40% of cases the diagnosis was established on the basis of only one abnormal value. This abnormal value was in the majority of cases at one hour during OGTT. In women with gestational diabetes HbA1c positively correlated with all theree glicemic values, with strogest correlation for the two hour glicemia (correlatioan coefficient of 0.6). In the control group only the 2 hour glicemua correlated with HbA1c (correlatioan coefficient of 0.79). Insulintherapy was indicated in 15% of cases, of which almost 80% had 3 abnomal values at the diagnosis. Three abnormal values at the moment of diagnosis were associated also with higher HbA1c values and with a higher number of C-sections.

Conclusion

In women with gestational diabetes mellitus three abnormal values on the diagnostic OGTT were associated with poorer pregnancy adverse outcomes. Three abnormal results in OGTT may indicate the need for an intesive intervention (frequent appointments, careful glucose monitoring, insulintherapy) and also for a multidisciplinary intervention (obstetrician, diabetologist, educator nurse, dietician, midwife, neonatologist and intensive care specialist).

Key words

Gestational diabetes, oral glucose tolerance test, pregnancy outcomes

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Hemodynamic evaluation in pregnant women with gestational diabetes

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Methods

A prospective case-control study was conducted on pregnancies referred to Maternal-Fetal Medicine unit, AOU Careggi, Florence, Italy since 2018 of GDM. Sixty-nine (69) singleton pregnancies with GDM and no pre-pregnancy comorbidities were included and compared with a control group of 60 physiological singleton pregnancies. Both groups underwent hemodynamic assessment by UltraSonic Cardiac Output Monitor (USCOM). Evaluations were performed in four gestational age intervals: 26-30 weeks (at diagnosis), 32-35 weeks and 36-39 weeks. In early GDM cases the first assessment was performed at 17-20weeks. We have considered six USCOM parameters: cardiac output (CO), cardiac index(CI), stroke volume(SV), total vascular resistance(TVR), inotropy index (INO) and potential to kinetic energy ratio (PKR).

Results

No differences were reported among the two groups regarding baseline constitutional characteristic (age, BMI, ethnicity, smoke, parity, ART). 72.1% of GDM women achieved a good metabolic control with insulin therapy. About perinatal outcomes in the studied population, there was only 1 case of pre-eclampsia (PE). Moreover, low rate of large of gestational age (LGA) (8.7%) and small for gestational age (SGA) (8,7%) fetus were reported. USCOM evaluation showed significant lower values of CO and SV than control group from the early third trimester (26-30weeks) until term ($p<0.001$). this difference can be already found at 17-21 weeks in early GDM cases versus controls but it is not significant ($p= 0.1$). instead CI is significantly lower in GDM group already at the first evaluation ($p = 0.002$). furthermore, we found higher TVR and PKR values and lower INO values in GDM group than in controls.

Conclusions

A hemodynamic maternal maladaptation to pregnancy can be detected in GDM women. In fact, a significant reduction in CO, CI, SV and INO and an increase in TVR and PKR in GDM versus no-GDM from 26-30 weeks until term was found. This difference can be already found at 17-21 weeks in early GDM cases versus controls but it less significant probably for the limited number of cases. The effect of hyperglycemia on vascular system or a poor pre-pregnancy CV reserve could explain the hemodynamic maternal maladaptation found in pregnancies complicated by GDM.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

First trimester gestational diabetes mellitus risk prediction

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Context
Gestational diabetes mellitus (GDM) remains a serious medical and social problem of our time, far from the final solution.

Objective
To identify the risk predictors of GDM and to develop a model of mathematical prognosis of the risk of the disease, suitable for use in the first trimester of pregnancy.

Materials and methods
The study and control groups were formed from among 1140 women. In addition to the standard examination, serum iron and glycated hemoglobin (HbA1) levels were measured in these pregnant women during registration. At the end of gestation, the study group included pregnant women with developed GDM (n=32), and 61 women with physiological pregnancy in the control group. The method of binary logistic regression was used to build a predictive model.

Results
Glucose level > 4.8 mmol/l in the study group was observed in 78.1%, in the control group - in 8.2% of women ($p<0.01$). When assessing the prognostic significance of HbA1c level for the risk of GDM development using ROC-analysis, its value at the cut-off point was 4.85% (at < 4.85% - low risk of GDM development, at ≥ 4.85% - high, $p<0.001$). When assessing the prognostic significance of serum iron level by ROC-analysis, its value at the cut-off point was 10.7 ng/ml (≤ 10.7 ng/ml - high risk of GDM, > 10.7 ng/ml – low, $p<0.001$). When assessing the prognostic significance of hemoglobin concentration for the risk of GDM by ROC-analysis, the hemoglobin level at the cut-off point was 109.5 g/l (≤ 109.5 g/l – high risk of GDM, >109.5 g/l – low, $p<0.001$). The prognostic model was developed using the binary logistic regression method: $P = 1/(1 + e\text{-}z) * 100\%$, $z = -54{,}8 + 0{,}19*X1 + 0{,}89*X2 + 4{,}3*X3 + 5{,}92*X4 – 0{,}2*X5 – 0{,}17*X6$, where P is the probability of the presence of GDM (%), X1 is the age of the woman (full years), X2 is the body mass index (kg/m^2), X3 is the serum glucose (mmol/l), X4 is the level of glycated hemoglobin (%), X5 is the serum iron content in the blood (ng/ml), X6 is the hemoglobin content in the blood (g/l). The obtained prognostic model was statistically significant ($p<0.001$). 50% was used as a separating value – with a value of P equal to or above 50%, a high risk of GDM was recognized, with values below 50% - a low risk of GDM.

Conclusion
The proposed mathematical model can be used for mathematical prediction of GDM.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Prevalence and patients' preferences regarding metformin administration in gestational diabetes management

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Context

Metformin is not routinely prescribed for the purpose of gestational diabetes mellitus (GDM) management. Various European medical societies recommend diet and insulin for glycemic control during pregnancy. However, both observational studies and randomized, controlled trials examined the effectiveness and short-term safety of metformin use in pregnancy. Moreover, oral administration instead of injections could lead to better compliance. This is why off-label prescription of metformin for GDM management is observed.

Objective

The aim of the study was to evaluate the prevalence of metformin administration among GDM patients along with GDMG2 patients' opinion regarding the preferred route of anti-diabetic medication administration.

Methods

It was a cross-sectional study. Data was collected by means of an anonymous, electronic questionnaire distributed among patients with the history of GDM.

Patients

One hundred fifty-six patients completed the questionnaire – 89 with GDMG1 and 67 with GDMG2. Respondents were between 19 and 44 years old (mean age: 30.6 years). Twenty-six (17%) were diagnosed with obesity, 16 (10%) with insulin resistance, and 20 (12%) with polycystic ovary syndrome before pregnancy. Metformin was prescribed to 19 (12%) patients prior to pregnancy.

Interventions

The only intervention required for the purpose of this study was voluntary and anonymous completion of an electronic questionnaire.

Main outcome measure

The main outcome measure was the prevalence of metformin use in GDM patients.

Results

Out of 156 patients, only three (1.9%) reported the continuation of metformin intake during the whole pregnancy. Four (2.6%) patients discontinued metformin use prior to conception. Twelve patients discontinued metformin intake between 4th and 15th gestational week.

Forty-four (66%) patients with GDMG2 indicated oral administration route as the preferred one in case of different anti-diabetic medication availability. Thirteen (19%) GDMGD2 patients stated that oral intake of hypoglycemic agents could contribute to longer professional activity during pregnancy.

Conclusions

Prevalence of metformin use in GDM is relatively low despite patients' interest in methods of glycemic control enabling oral drug administration. More data on the long-term safety of metformin use in GDM is needed.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Oxidative and antioxidative status in pregnant women with different types of diabetes mellitus

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Context
Diabetes mellitus (DM) is linked with an increased risk of fetal and maternal complications. Hyperglycemia generates advanced glycation end products and reactive oxygen species that increase the level of oxidative stress (OS). Despite many reports, regarding the OS problem in gestation, there is still a lack of these data in case of diabetic pregnancy.

Objective
To evaluate the serum concentration of nitrotyrosine, 8-isoprostane and the total antioxidant capacity (TAC) in women with type-1 DM (T1DM), type-2 DM (T2DM), gestational diabetes mellitus (GDM) and a healthy group in the 1st and 3rd trimesters.

Methods
It was a prospective cohort study. The study groups were formed: T1DM (group I-non-planned pregnancy (n=20); group II-planned (n=20), T2DM (group III-diet (n=20); group IV-insulin (n=20); GDM (group V-diet (n=20); group VI-insulin (n=20); control n=15 (VII). The determinations of nitrotyrosine, 8-isoprostane were measured using ELISA by Cayman Chemical kits. The evaluation of these factors was performed at gestational weeks 11-14 and 30-34.

Results
In the first and third trimesters of pregnancy the maternal serum nitrotyrosine concentrations (mcg/ml) were significantly higher in T1DM groups: I (1st- 16.4; 3rd-37.1), II (1st- 13.9; 3rd-17.4), and T2DM insulin group - IV (1st-11.5) - compared to the control group (1st-8.06; 3rd- 6.9) (F1=8.34, F3=7.22, p=0.001). The levels of 8-isoprostane (mcg/ml) had the same trends and were higher in pre-gestational types of DM: I (1st-641.5; 3rd–473.8), II (1st-408; 3rd-263); III (1st-358.2; 3rd-309.1), IV (1st-492.3; 3rd-213.4) compared to the control group (1st-141.4, 3rd-91.5) (F=5.43, p=0.01). In GDM insulin group the levels of the mentioned factors were lower than in DM groups, but higher than in the control group (12.1; 380.4). TAC (mcg/ml) was the lowest in the non-planned T1DM (1st-0.83; 3rd-0.92) and T2DM insulin (1st-0.9; 3rd-0.93) compared to the control group (1st-1.19; 3rd-1.23) (F=2.79, p=0.029). Additionally, we found direct and indirect correlation links between levels of 8-isoprostane, TAC and HbA1c levels in the first trimester of pregnancy (r=0.39, p=0.02; p=-0.49, p=0.001).

Conclusion
Any type of DM during pregnancy is associated with OS. The levels of nitrotyrosine and 8-isoprostane increase towards the end of the term and are directly connected with the glycemic control. On the contrary, the concentrations of TAC decrease progressively and more in severe forms of diabetes.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

The maternal IGF-system in diabetic pregnancy: a link to fetal macrosomia

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Context
The insulin-like growth factor (IGF) axis is an important regulator of fetal development. Diabetes mellitus (DM) is associated with an abnormal fetal growth. The IGF axis could play a major role in this process.

Objective
To evaluate the serum concentration of insulin growth factors (IGF-I, II) and binding protein (IGFBPs) in women with type-1 DM (T1DM), type-2 DM (T2DM), gestational diabetes mellitus (GDM) and a healthy group in the first and third trimesters of pregnancy.

Methods
It was a prospective cohort study. The following study groups were formed: T1DM (group I - non planned pregnancy (n=20); group II - planned (n=20), T2DM (group III - diet (n=20); group IV - insulin (n=20); GDM (group V - diet (n=20); group VI - insulin (n=20); control n=15 (VII). Free IGF-I, IGF-II and total IGFBPs-1, 3, 6, 7 determinations were measured using MILLIPLEX MAP human panel kits (Millipore, USA). The evaluation of these factors was performed at gestational weeks 11-14 and 30-34.

Results
In the 1st and 3rd trimesters of pregnancy the maternal serum IGF-I concentrations (ng/ml) were significantly higher in DM groups: I (1st- 49.3; 3rd – 36.7); II (1st- 31.1; 3rd – 43.4); III (1st-31.1; 3rd- 40); IV (1st-26.57; 3rd – 31.2); V (3rd – 22.6); VI (3rd – 27.1) compared to the control group (1st-21.3, 3rd-18.0) (F=11.1, p=0.001). The concentration of IGF-II (ng/ml) had the same trend: I (1st-181.8; 3rd–152.1), II (1st-109.2; 3rd-157.5); III (1st-139.8; 3rd-119.6), IV (1st-98.67; 3rd-99.2); V (3rd – 104.6); VI (3rd – 99.5) compared to the control group (1st-82.4, 3rd-90.5) (F=9.43, p=0.001). The highest expression of these biomarkers was observed in women with more severe metabolic disorders (non-planned T1DM, insulin therapy requirements). The IGFBP-1 levels (ng/ml) were significantly lower in all DM groups: 1st trimester (IQR 8.7-11.2), 3rd (IQR 4.2-7.2) compared with a non-diabetic group (1st-16.4; 3rd – 10.5). We did not find any differences between the groups in the level of total IGFBP-3, 6, 7. Additionally, we found direct correlation links between IGF-I concentrations and fetal weight (r=0.69, p=0.001).

Conclusion
In the first and third trimesters of pregnancy, the pre-existing DM and GDM are associated with higher IGF-I, IGF-II and lower IGFBP-1 levels in maternal serum. Alterations in circulating IGF and IGFBPs may alter birthweight and lead to the development of macrosomia and metabolic disorders later in life.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Elevated concentrations of soluble leptin receptor and relative insulin resistance in Small for Gestational Age (SGA) twins

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Contex

Leptin administration has been demonstrated to induce hypoglycaemia, while hypoglycaemia is particularly dangerous for SGA fetus. Circulating soluble leptin receptor (SLR) binds excess leptin, thus inhibiting leptin signalling through diminished leptin binding to signal-transducing membrane receptors. Intrauterine Growth Retardation (IUGR) may increase future risk of insulin resistance, glucose intolerance and type 2 diabetes.

Objective

We aimed to assess whether leptin system and glucose homeostasis are altered in SGA versus appropriate for gestational age (AGA) twins.

Patients & methods

At delivery, we have assessed concentrations of fetal leptin, SLR, glucose and C-peptide in 32 dichorionic twin pregnancies, where the weight of the twins differed by>15%. In addition, one twin was small for gestational age (<10th percentile-SGA) (IUGR) while the other was appropriate for gestational age (>10th percentile-AGA).

Results

Though, there was no difference in leptin concentrations between SGA and AGA twins (p=0.37), the concentrations of SLR were significantly higher in SGA twins [mean & 25-75 percentile range: 28.63 ng/ml (19.64-35.82) vs 19.91 ng/ml (15.83-24.21), p<0.01]. The opposite situation pertained to maternal placentas, i.e. higher concentrations of leptin in placentas of SGA twins [130.1 pg/100g total protein (91.6-246.6) vs 83.8 pg/100g total protein (56.8-140.7), p=0.03], despite the lack of difference in placental SLR (p=0.66). SGA twins also demonstrated higher C-peptide concentrations [44.48 pmol/l (28.48-129.13) vs 20.91 pmol/l (7.17-77.14), p<0.05], with no difference in glucose concentrations (p=0.49). Furthermore, in SGA twins there were also higher values of [peptide C]x[Glucose] product (HOMA-IR equivalent): 249.3 pmolxmmol/l (150.6-1010.5) vs 129.4 pmolxmmol/l (50.7-475.4), p=0.045, that confirmed an increased insulin resistance in SGA twins.

Conclusions

In the setting of an identical maternal environment, SGA twins demonstrate higher concentrations of soluble leptin receptor and increased insulin resistance in comparison to their AGA sibling. We speculate that this might represent a protective mechanism against potential leptin-induced hypoglycaemia. It remains to be confirmed, whether fetal insulin resistance in SGA twins might influence future susceptibility towards glucose intolerance and type 2 diabetes.

Acknowledgement

Supported by the Grant No. 2014/15/B/NZ5/03495 by The National Science Center (NCN), Poland.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Effect of exogenous sex hormones administration on the course of intrahepatic cholestasis of pregnancy

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Context
A possible undesirable effect of sex hormones administration during pregnancy is their potential adverse effect on the liver. The most common liver pathology associated with pregnancy is the intrahepatic cholestasis of pregnancy (ICP).

Objective
The aim of the study is to assess the effects of female sex hormones administration during pregnancy on the course and effectiveness of ICP treatment.

Methods-patients
The study included 97 patients with ICP. Exogenous hormonal effects were the use of assisted reproductive technologies (ART) and/or estrogen and progesterone administration during pregnancy.
Patients were performed clinical, laboratory examination, including assessment of the level of antioxidant enzymes (superoxide dismutase, glutathione peroxidase). The intensity of skin itching was estimated from 0 to 3 points. Patients were treated with ursodeoxycholic acid (UDCA) at a dose of 500-2000 mg till to delivery.

Results
More than half of patients with ICP (62.89% CI: 53.7%-71.3%) took sex hormone medications or had a pregnancy after ART. In pregnancies after using ART, ICP developed at a significantly earlier stage than in patients which conceived naturally (p=0.001). The use of sex hormones related to a high rate of cholestasis recurrence after its regression during treatment (p=0.001). Intake of sex steroids (p=0.005) in patients with ICP was associated with the more frequent development of preeclampsia and more often indications for caesarean section (p=0.003). Sex steroids administration positively correlated with severity of skin itching (p=0.017) and negatively - with the serum levels of antioxidant enzymes (p=0.018).

Conclusions
The exogenous sex hormones administration contributes to the earlier manifestation of ICP, its recurrence during treatment of UDCA, greater severity of itching, antioxidant protection disorders and preeclampsia. Pregnant women taking sex hormone medications and/or having pregnancies after ART should be screened for early detection of ICP.

Pregnancy: gestational diabetes mellitus, multiple pregnancies, immunologic and endocrine disorders

Novel molecular biomarkers involved in Gestational Diabetes Mellitus(GDM)

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Background

About 1–2% of all pregnant women develop an abnormal glucose tolerance in pregnancy. This condition is called gestational diabetes mellitus (GDM). prognosis and clinical management of GDM is one of the subjects of great interest among GDM researchers. In this study we described recently identified molecular biomarker involved in GDM.

Method

Eligible studies were searched at diabetes research center, Shahid Sadoughi University of medical sciences in PubMed, Scopus, Google Scholar and web of Science by considering the keywords such as “diabetes mellitus”, “biomarker”, “microRNA”, “diagnostic tool” and “clinical manifestation”.

Result

A total of 107 studies were finally included in our review. After evaluating numerous articles including original, meta-analysis and review we focus on molecular biomarker that are involved in diagnosing and management of GDM.

Conclusion

increasing interest in biomarkers relating to GDM, goes back to its role in decreasing diabetes-related morbidity and mortality. This study emphasizes on major molecular biomarkers including proteomic and microRNA (miRNAs) as a novel and interesting GDM biomarkers. Thus, these biomarkers help us to achieve timely diagnosis of GDM.

Endocrine disorders and women health, endocrine dysruptors

The effect of genomic and post-genomic factors on ovarian reserve in type 1 diabetes

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Context

Accelerated aging is a characteristic for patients with type 1 diabetes mellitus (DM1), so manifestations are not only in the increased frequency of cardiovascular events, but also in decreasing of ovarian-menstrual function, in the earlier onset of menopause. It has been shown that the decreasing of the reproductive function in patients with DM1 may be associated with a decrease in the ovarian reserve. Premature aging is frequently observed among individuals with DM1.

Objective

To evaluate the ovarian reserve function in female patients of reproductive age with DM1 in comparison with healthy women.

Methods

Anthropometrics, analysis of serum hormone concentrations.

Patients

224 Caucasian women, aged 20-30 years with DM1 and 230 healthy women of comparable age.

Interventions

Serum levels of anti-Mullerian hormone (AMH), inhibin B, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, and testosterone were examined on the 2-3 day of menstrual cycle.

Main outcome measures

Ovarian volume and antral follicle count (AFC) were measured by ultrasound. Glycated hemoglobin level (HbA1C) and a number of a CGG repeat in FMR1 gene were evaluated.

Results

We revealed statistically significant difference in the following parameters in diabetic women in comparison with healthy women: AMH, AFC and HbA1C. However, in diabetic and healthy patients parameters remained within reference ranges. There was strong negative correlation between HbA1C and AMG levels. There were no differences between a number of a CGG repeat in FMR1 gene in diabetic patients and healthy women.

Conclusions

Ovarian reserve function parameters decrease in women with DM1 in comparison with healthy women, but ovarian reserve parameters are in normal reference range. These findings are important in pregnancy planning consulting by gynecologists and endocrinologists. We should recommend women with DM1 to plan a pregnancy as soon as possible and to use the assisted reproductive technology in cases of an absence of natural pregnancy. This work was supported by the Russian Science Foundation under Grant №17-75-30035.

Endocrine disorders and women health, endocrine dysruptors

Estetrol elicits a metabolic protection against obesity and associated arterial diseases

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Context

Estetrol (E4), a natural estrogen synthesized by the human fetal liver, is currently evaluated in phase III clinical studies as new menopausal hormone therapy. Indeed, E4 significantly reduced the frequency of vasomotor symptoms and have beneficial effect on bone metabolism and genito-urinary syndrome. Oral E4 was found to have limited effects on coagulation factors in the liver of women, suggesting a safer venous thrombotic risk profile compared to classic oral estrogens.

Objective

The aim of this study was to evaluate the effect of E4 on metabolic disorders, which increases significantly after menopause.

Methods and Results

First, E4 significantly reduced body weight gain and adiposity and improved glucose tolerance in response to a western diet (42% kcal fat, 0.2% cholesterol) in ovariectomized WT female mice. Second, in atheroma prone LDLR-/- mice, E4 also prevented disorders associated to obesity such as atherosclerosis and liver steatosis. Third, we evaluate the role of hepatic ERα in these beneficial actions of E4. To this aim, mice harbouring a hepatocyte-specific ERα deletion (LERKO) were bred with LDLR-/- mice. E4 still prevented obesity and atherosclerosis in these LERKOLDLR-/- mice, but E4-protection against lipid deposition in the liver was abrogated in mice.

Conclusion

To conclude, E4 could thereby confer metabolic protection against obesity and associated arterial diseases.

Endocrine disorders and women health, endocrine dysruptors

Reliability and validity of the Japanese version of dairy records of severity of problems

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Context
To make a diagnosis of premenstrual syndrome (PMS), we developed the Japanese Version of Daily Records of Severity of Problems (J-DRSP), and assessed its basic psychometric properties, i.e. the concurrent validity and internal consistency. Moreover, we developed the smartphone application named "DRSP-JAPAN" in which the DRSP items were rated every day.

Objective
We aimed to demonstrate the test- retest reliability and factorial validity of J-DRSP using DRSP-JAPAN app.

Participant(s)
We recruited participants from November 2018 to March 2019. They were students and staffs at Kyoto University School of Public Health and Doshisha Women's College of Liberal Arts, and patients at Kyoto University Hospital and some gynecology clinics.

Methods
Participants answered J-DRSP every day using DRSP-JAPAN between CD-7 and CD+10 (i.e. between 7 days before the onset of menstruation and 10 days after it). The recorded data were stored on the database server through the Internet. We demonstrate the factorial validity: the confirmatory factor analysis (CFA) was performed using 21 symptom items in J-DRSP of the day before menstruation. We also demonstrated the test- retest reliability: intraclass correlation coefficients (ICCs) were calculated for the total score J-DRSP for a follicular phase (CD+9 vs. CD+10) and a late-luteal phase (CD±0 vs. CD-1).

Result(s)
DRSP-JAPAN app was downloaded by 304 women who reported regular menstruation and were not taking any psychotropic or hormonal agents. Among them, we analyzed 243 women who recorded more than 3 days during each one week of a luteal phase (CD-6 to CD±0) and a follicular phase (CD+4 to CD+10). The result of CFA supported the two-factor structure (psychological and physical factors) The Cronbach's alpha of each domain was 0.95 and 0.84, respectively. ICC for a follicular phase and a luteal phase were 0.76 and 0.60, respectively.

Conclusions
J-DRSP provides reliable and valid measures of premenstrual symptoms in Japanese women. With acceptable psychometric properties, J-DRSP can be used in future research in Japan.

Endocrine disorders and women health, endocrine dysruptors

Sexual function in women with androgen excess disorders: classic forms of congenital adrenal hyperplasia and polycystic ovary syndrome

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Context
Women with androgen excess disorders (AED) have been found to have impaired sexual functions, however it is unclear, whether sexual functions differ depending on the cause of AED.

Objective
To compare sexual function in women with AED of different origins: classic forms of congenital adrenal hyperplasia (CAH) and polycystic ovary syndrome (PCOS) in context of sociodemographic, clinical, hormonal and metabolic findings.

Methods
84 women (21 with CAH, 63 with PCOS) aged 18-40 years were included into the study. All participants completed a questionnaire regarding their sociodemographic background and underwent anthropometric measurements. Hirsutism was evaluated according to Ferriman-Gallwey score, alopecia using Ludwig scale, acne was noted but not scored. Plasma levels of total testosterone (TT), androstenedione (A) and 17-hydroxyprogesterone (17OHP) were measured with immunoassay. Free testosterone level was calculated. For the assessment of sexual functions, the Female Sexual Function Index (FSFI) questionnaire was applied.

Outcomes
Difference in sexual function between CAH and PCOS women.

Results
Apart from the higher physical activity in PCOS patients (P=0.017) we found no significant sociodemographic differences between the two groups. In clinical assessment, women with CAH had a lower incidence of acne (P=0.006). Their plasma levels of 17OHP (P=0.005) and insulin resistance index (P = 0.0248) were higher, while total testosterone (P=0.049) and glucose (P=0.006) lower compared to the PCOS group. Significantly more women with CAH compared to the PCOS patients were homosexual (23.8% vs 3.17%, P=0.003) and bisexual (19.04% vs 0%, P=0.006). CAH group showed a lower total FSFI score (P=0.0043) and lower scores in three from five particular domains: lubrication (P=0.0131), sexual satisfaction (P=0.0006) and dyspareunia (P<0.0001). Higher physical activity was associated in all women with higher total FSFI score (P=0.013) and scores in the domain of orgasm (P=0.04) and sexual satisfaction(P=0.008), in CAH women also in the domain of pain (P=0.03). There were no correlations between sexual function and clinical and laboratory markers of hyperandrogenism, anthropometric measurements, metabolic profile and demographic characteristic.
Clinical Implications: Expert medical care should be provided to patients with CAH to avoid sexual dysfunction.

Conclusions
The sexual function of CAH women is impaired in comparison with PCOS patients.

Endocrine disorders and women health, endocrine dysruptors

The impact of period symptom tracker at female patients with psychiatric disorders

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Context

Exacerbation of certain medical conditions is a well-recognized phenomenon at specific phases of the menstrual cycle.
Mood symptoms are sometimes accompanied by a somatic component: which can show circa-menstrual and/or circa-ovularory appearence. The best known disorder is the premenstrual syndrome with its characteristic somatic and mood changes. Even smart phone applications are accessible for period syptome tracking. Although it is common to have one or a few premenstrual symptoms, clinically significant PMS occurs in 8 percent of women. The clinically most significant form is Premenstrual Dysphria Disorder (PMDD) which affects approximately 2 percent of women.

Objective

To study if there is a temporal pattern of complains, to decide wether an additional hormonal treatment needed.

Method

In our private outpatient women's health department a paper based scale was used as a symptome tracker to assess longitudinal pattern of premenstrual syndrome for two months with PMS Symptom Tracker
If any other condition is was suspicious, we used a disease-specific checklist for additional two months.
MHCC PMDD - chart: Every women was asked to complete the chart for 2 month
PTSD CheckList – Civilian Version (PCL-C) was completed by 4 women who had additional symptoms to the primary checklist
No new psychotic patient was presented in the outpatient clinic in this time interval.
Patients From January 2018 to December 2019. 46 women,18-40 year old were included at the gynecological outpatient clinic with the complain being depressed and/or angry and it was suspected to be connected to their period by self diagnosis. Contraceptive pill or intrauterin levonorgesterel system using patients were nor excluded.

Results

32 of the 46 patients (69.5 %) completed the two months chart. Complains of 11 of 32 women (34.37%) was not stricly periodical, but severe enough to be treated - psychoterapy and/or medication. 21 (65.6%) women had periodical pattern on the chart. 8 of them had periovulatory symptoms as well. 3 of the 4 PTSD patients had cyclical pattern. One of them had midcycle exacerbation in the midcycle, however she used contraceptive pill.

Conclusion

If a woman's history is suggestive of significant periodical condition, then accurate documentation should be obtained using a menstrual calendar. The results can help to find the appropriate management:
- cyclic modulation of therapy menstrual cycle–related changes in the disease process.
- data of the present pivotal study suggest, tracking methods can provide meaningful contribution to identify more accurate phenotype of PMD, to optimize interventional strategy:
- hormonal therapy with estrogen and/or special gestagens
- ovulation suppression with oral anticontraceptive pill –with special estrogen and gestagen components - may be warranted.
- we can find data of the success of GnRh-agonist or medroxy progesterone acetate medication in the literature, but we did not find it successful.

Endocrine disorders and women health, endocrine dysruptors

Risk factors for gestational diabetes mellitus in women with hypothalamic dysfunction

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The aim of our study was to establish significant risk factors for the development of gestational diabetes mellitus (GDM) in women with hypothalamic dysfunction (HD) and metabolic disorders in the pubertal period to predict adverse pregnancy outcomes.

Design

We conducted a prospective examination of 170 adolescent girls with HD in the puberty. Body mass index (BMI) corresponded to overweight in 66 (38.8%) adolescent girls with HD, obesity was in 104 (61.2%) 31.1 (0.35) kg / m^2. The mean follow-up was 4.7 (1.7) years. The study included 86 women of reproductive age out of 170 teenage girls with DG. We evaluated the risk factors for GDM in 72 pregnant women. The study was supported by a grant from the Russian Foundation for Basic Research, project No. 19-013-00781.

Methods

The glucose content was determined for all pregnant women in the period of 7–8 weeks and 24–25 weeks in fasting venous serum after 8–12-hour fasting by an enzymatic glucose oxidase method with orthotolidine oxidation. The oral glucose tolerance test included the determination of glucose in fasting venous blood and 120 minutes after an oral glucose load of 75 g. Values for the diagnosis of GDM: fasting blood glucose levels in venous blood plasma> 5.1 <7.0 mmol / L or after 2 hours > 8.5 mmol / L

The risk of GDM development was found in adolescents from single-parent families (RR - 2.3; 95% CI: 0.74–7.31), low-income families (RR - 1.2; 95% CI: 0.41–3.67) smoking (RR - 1.2; 95% CI: 0.31–4.95), obesity (RR 1.32; 95% CI: 0.42–4.12), abdominal obesity (RR 2, 2; 95% CI: 0.31–15.7), preeclampsia in their mother during pregnancy (RR - 1.9; 95% CI: 0.64–5.5), anemia (RR - 1.7; 95% CI: 0.52–5.5), asphyxia at birth (RR - 1.14; 95% CI: 0.37–3.52). A significant risk factor for the development of GDM was diabetes in the immediate family (RR - 9.6; 95% CI: 3.7–18.3).

The risk of developing GDM in women in reproductive growth: waist circumference> 80 cm (RR - 1.6; 95% CI: 0.52–4.84), BMI> 24.9 kg / m^2 (RR - 1.5; 95 % CI: 0.49-4.5). A significant risk factor for GDM was induced pregnancy (stimulation of ovulation or IVF) (RR - 3.16; 95% CI: 1.11–8.97). Vaginal administration of gestagens during pregnancy increased the risk of GDM, but was not statistically significant (RR - 1.4; 95% CI: 0.47–4.1).

Endocrine disorders and women health, endocrine dysruptors

Frequency of reproductive endocrine complications in women with epilepsy

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ANMRC

Epilepsy is one of the most widespread diseases of the nervous system with a negative influence on all aspects of the patient's life. More than 2, 4 million new cases of epilepsy arise every year around the world. Reproductive health had gained great social value in connection with the aggravated problem of quality and quantitative reproduction in population. Women in reproductive age make from 25 to 40% among patients with epilepsy. Antiepileptic drugs (AEDs) and seizures had a negative effect on reproductive health (RH). However, studying of AEDs influence on reproductive health in the international clinical trials hadn't obligatory

Objective

To study the frequency of reproductive endocrine complications (REC) due to antiepileptic drugs in mono - and polytherapy in women with epilepsy (WWE).

Methods

This work was a part of prospective observation research of AEDs side effects studying on RH at 155 WWE into 3 groups of therapy type. The 1gr.- monotherapy, 2gr.-polytherapy of AEDs, 3gr. - without AEDs. Inclusion criteria were the reproductive age from 16 to 45y.o. The gynecologic diagnosis was made in compliance with ICD-10. Definition of interrelation "AEDs - reproductive endocrine complications (REC)" was carried out by means of algorithm Naranja.

Results

68 patients (44%) consisted in1gr, 67 (43%) - in 2 gr, 20 (13%) - in 3 gr. The average age made 25y.o. Statistically reliable differences in qualitative characteristics of groups weren't taped. The common frequency of RH pathology made 53%. Comorbid pathology was noted in 13%. REC due to AEDs side effects made 40%. Polytherapy enlarged REC frequency in comparison with other groups (1gr.- 30%, 3gr-10%) and made 60% ($p < 0{,}001$). Reproductive endocrine complications due to AEDs were often represented by reversible side effects in clinical outcomes (57%).

Conclusions

Reproductive endocrine complications were a frequent side effect of antiepileptic drug therapy in women with epilepsy. Maximal frequency of reproductive health disturbances was at antiepileptic drugs polytherapy. Neurologists and gynecologists must monitor reproductive health in women with epilepsy.

The reported study was funded by Russian Foundation for Basic Research (RFBR) according to the research project № 18-013-00222.

Endocrine disorders and women health, endocrine dysruptors

Effect of exposure to Bisphenol A in the thickness of uterine layers in the vesper mouse

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Context

It is well known that Bisphenol A (BPA) is a substance used in the production of polycarbonate and epoxy resins that acts as an endocrine disruptor. The vesper mouse (Calomys laucha) is a small wild rodent found in South America, which is used in research for its genetic variability and resistance to stressful agents. As it lives on coasts, pastures and along roadsides, it may be affected by environmental sources of BPA and therefore act as a bioindicator for the effects of endocrine disruptors in humans.

Objective

The goal of this study was to verify the effects of BPA in litter parameters and uterine layer thickness of C. laucha.

Methods

Sixty C. laucha females of 50-70 days old received by gavage during pregnancy the following substances: olive oil (negative control) or BPA (40, 80 or 200 µg/Kg). After birth, pups were counted and sexed. Mothers were euthanized after lactation period. Female offspring were euthanized on PND 70, after reaching full maturation of the reproductive tract. Uteri were processed for histology. Measurements for myometrium, endometrium and total uterine thickness (n=10 mothers and 10 offspring) were performed using ImageJ software.

Results

Of all sixty females, 41 sired litters. One animal from the BPA40 group was born dead and without three limbs. Two animals from the BPA80 group presented male genitals and female reproductive tract. Proportion of gender per treatment was 1:1 in all groups. Number of pups per litter showed no differences ($p<0.05$) between the groups, with a mean of 3.8 ± 0.31 females and 2.2 ± 0.48 males. Uteri from one animal of BPA40 and four animals of BPA80 offspring groups presented edema when removed, as well as from two mothers of BPA80 group. In mothers, BPA40 significantly increased ($p<0.05$) total and endometrial layers, while BPA80 and BPA200 reduced all uterine layers. In offspring, BPA40 reduced all uterine layers, while BPA80 showed no significant difference and BPA200 reduced endometrium and increased myometrium layers.

Conclusions

BPA did not affect the number and gender of pups per litter, but caused malformation and disturbed sex differentiation. Adult and fetal exposure to BPA differently affected the uterine layers of vesper mice. This study showed that adult and in utero exposure to BPA has long-term effects in this species and these alterations might affect fertility of the animals. Such findings offer valuable insight of BPA effects in women.

The climacteric syndrome

Lipid profile in menopausal women with hot flashes

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Context

Hot flashes are one of the first clinical symptoms of the menopause. They occur as a result of changes in the concentrations of sex hormones that happen during the menopause that leads to thermoregulatory dysfunction. Hypoestrogenism in menopause also leads to hypertension and hypercholesterolemia which impairs endothelial function by enhancing inflammatory reaction, lipoprotein oxidation and prothrombin changes. These changes favor the onset of atherosclerosis and increase the risk for cardio vascular diseases.

Objective

The aim of this study was to determine associations between hot flushes and lipid profile in menopausal women.

Methods

The study involved 75 menopausal women divided into two groups: in first group there was 48 menopausal women with hot flushes, average age 52.02 ± 4.25 years, average body mass index 24.54 ± 2,75 kg/m^2 and mean menopausal period 3.35 ± 2,28years. In second, control group there was 27 menopausal women without hot flushes, average age 54.00 ± 4,42 years, average body mass index 26.49 ± 3,92 kg/m^2 and mean menopausal period 4,70 ± 3,98 years. Data on the presence of hot flashes were based on history data. Venous blood samples were collected for analyses of blood cholesterol (Chl), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (Tg), apolipoprotein A-1, apolipoprotein B, lipoprotein(a),

Results

Women with hot flashes had significantly higher values of HDL (1,64 ± 0,44 mmol/L vs 1,42 ± 0,26 mmol/L; p<0,05) compared to women without them. There was no statistically significant difference between mean values of cholesterol (6,34 ± 1,27 mmol/L v.s. 6,10 ± 1,10 mmol/L; p>0,05), LDL (4,01 ± 1,17 mmol/L v.s. 4,20 ± 1,04 mmol/L; p>0,05), Tg (1,45 ± 0,65 mmol/L v.s. 1,45 ±0,46 mmol/L; p>0,05), apolipoprotein A-1 (1,68 ± 0,31 g/L v.s. 1,55 ± 0,26 g/L; p>0,05), apolipoprotein B (1,31 ± 0,42 g/L v.s. 1,24 ±0,36 g/L; p>0,05), lipoprotein(a) (0,20 ±0,21 g/Lv.s. 0,24 ± 0,28 g/L; p>0,05) between compared groups

Conclusions

We have found that women with hot flushes had higher levels of HDL than women without them. Considering the fact that hot flashes are associated with poorer lipid profile and cardiovascular risk, further studies should be performed on larger number of menopausal women.

The climacteric syndrome

Is there an association between joint/muscular discomfort and sarcopenia in climaterics? Valuation in women of Colombian Caribbean

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Context
Joint/muscular discomfort (JMD) is common among middle-aged Colombian Caribbean women. There are not enough studies that address the association between this symptom and the clinical criteria of sarcopenia (CCS).

Objective
Estimate the association between JMD and CCS in climacteric women.

Methods
Cross-sectional study that is part of the research project CAVIMEC (Quality of Life in Menopause and Colombian Ethnic Groups). Anonymous and voluntary participation, approved by the ethics committee of University of Cartagena, Colombia. Two groups were formed: with JMD (score greater than zero on the eleventh question of the MRS) and without JMD (zero score). Data are expressed as Me [IQR] for continuous data, and percentages for categorical data.
The significance of the differences between groups was established according to homogeneity of the variance. Logistic regression was performed with JMD (independent variable) and CCS (dependent variable).

Patient (s)
Healthy Colombian Caribbean women. 40-59 years old. Identified at home. Pregnant, physically disabled, cognitive disorders, diagnosed degenerative muscle pathology, collagen or neoplastic pathology were excluded.

Interventions
A form of sociodemographic characteristics was applied and Menopause Rating Scale. Anthropometrics measurements were recorded: weight, height, waist circumference, calf circumference, grip strength of the skillful hand (dynamometer) and speed test. European Working Group on Sarcopenia in Older People criteria were applied to determine CCS.

Main outcome measure (s)
JMD, muscle mass, muscle strength, physical performance and sarcopenia.

Outcomes
403 women were studied, age 48 [45-54], BMI: 25,9[23,4-28,7], and 44.5% were postmenopausal. 256 (63,5%) with JMD and 147 (36,5) without JMD.
Women with JMD had lower muscle mass, muscle strength and gait speed (p<0,005), also more presence of CCS: 10,9%[95%CI:7,3-15,4] compared to 2,7% [95%CI:0,7-6,8] p=0,003. JMD was associated with low muscle mass OR:3,4[95%CI:1,4-8,5], decreased muscle strength OR:3,5[95%CI:1,8-6,7], lower physical performance OR:5,1[95%CI:1,5-17,5] and sarcopenia OR:4,3[95%CI:1,5-12,7].

Conclusion
JMD was significantly associated with low muscle mass, decreased muscle strength, lower physical performance and CCS.

The climacteric syndrome

Vita Nova: an adaptive system to reduce cardiovascular risk in pre-menopausal and menopausal women

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Context

Menopausal transition represents one of the moments of greatest health change and psychological fragility for the women.

Objective

The new app developed by the Vita Nova consortium aims to collect and systematize the factors that characterize the profile of each woman. On the basis of the carried out analysis, the app outlines behavioral change paths during the menopausal transition.

Methods - Patient(s)

The population sample was composed by 25 women from 46 years that used the "Vita Nova assistant version 1.0.0" application together with the FitBit charge2 physical movement detection device.
Metabolism and cardiovascular risk was assessed at enrollment by measuring and asking for specific indicators.
Different questionnaires were then submitted to the volunteers:

- Women's Health Questionnaire (WHQ
- Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)
- Clinical, socio-economic and psychological setting of the users.

Main outcome measure

At the end of the experimentation, the Self Usability Scale.

Result(s)

- Food habits: improvement in the quality of food, with an statistically significant increase in the consumption of "healty" foods and the detriment of "junk food" and sugary drinks (p=0,046).
- improvement in the perception of the symptomatologic sphere typical of the perimenopausal transition
- Physical activity: there was a positive trend in patients with a net increase in the amount of sport dedicated time
- From the WHQ
- Presence of anxious and depressed behavior: the data show an improvement in the mood
- General well-being: greater perception of physical fitness and greater perceived physical performance
- Somatic symptoms: overall overlapping results
- Memory and concentration: clear significant implementation of the self-perception of these two domains was detected (p=0,038)
- Vasomotor symptoms: the situation was stationary
- Problems related to sleep: improvement in the quality of sleep

Usability of the system: All patients responded positively to a score near or above 68 was obtained.

Conclusions

The Vita Nova app is adaptive service that can help women in restoring a state of well-being during menopausal transition.

The climacteric syndrome

Prevalence of bad sleeping in climacteric women from the Caribbean Colombian, according to presence of feelings of panic. Assesment using the Pittsburugh's Sleep Quality Index

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Context
Sleeping characteristics, feelings of panic (FP), anxiety or o inner restlessness, must be assessed in the climacteric.

Objetives
To estimate the prevalence of bad sleeping and the components of sleep, in climacteric women, according to the presence of FP.

Methods
Cross-sectional study which is part of the investigation project CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas). Anonymous and voluntary participation, approbation of the ethics committee, Universidad de Cartagena, Colombia. Epiinfo-7 was used. Quantitative variables are presented in means and standard deviation, qualitative ones in absolute values and percentages. Logistic regression was used: the quality of sleep was taken as the dependent variable and the sociodemographic characteristics, adjusted to the FP, were the independent variables.

Patients
Women residing in Colombian Caribbean, with ages between 40-59 years old, healthy, enlisted by pollsters outside of hospital facilities.

Intervention
A form of the sociodemographic characteristics, the Menopause Rating Scale (MRS), to identify FP through six items, and Pittsburgh's Sleep Quality Index (PSQI), which stablishes the quality of sleep, a higher punctuation meaning a worse quality of sleep.

Results
412 women were studied, with a mean age of 49,2±4,9 years old. 54 (13,1%) informed FP and 358 (86,9%) denied it. No differences were observed between the groups in terms of menopausal status, body mass index, work activity, diabetes and arterial hypertension. Women with FP used more hormonal therapy than those free of FP (p=0,006). Cronbach alpha PSQI: 0,85. The PSQI score was higher in women with FP than without it. 7,0 ± 3,3 vs 4,4 ± 1,0 (p <0,001). All components of PSQI (subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, day time dysfunction) had a higher score in women with FP (p<0,05). Bad sleep was observed in 178 (43,2%) of the women studied, in 41 (75,9%) with FP and in 137 (38,3%) without FP (p<0,05). Coffee consumption was associated with a higher frequency of FP, OR:2,4 [95%CI:1,2-4,9] and aerobic exercise with lower FP, OR:0,3 [95%CI: 0,1- 0,8].

Conclusions
In climacteric women of the Colombian Caribbean, it was observed that four out of ten had poor sleep, the proportion being higher among those with FP.

The climacteric syndrome

Menopause prevention of reproductive decline with an evolutionary lifestyle

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Liberi professionisti

Context
Menopause is a consequence of reproductive aging and follicular depletion (ovarian failure), yielding very low circulating estrogen serum concentrations and biologically disadvantageous metabolic alterations: late postmenopausal osteoporosis, cardiovascular disease and cognitive decline.
Evolutionary medicine generally seeks to unify emerging health issues and their genetic antecedents, here we focus on diseases appearing during the post-reproductive period that are no longer subjected to the fitness-selecting forces of evolutionary biology
Analyzing the fundamental underlying physiology that characterizes the postmenopause reveals many characteristics that are biologically disadvantageous when sustained over time. An evolutionary medicine perspective calls for reassessing the current approach that discourages the use of estrogen support in menopause. A methodical evolutionary medical inquiry may generate options that not only lengthen disease-free life spans but also improve quality of life
The signs and symptoms of menopause are affected by dietary, exercise, and reproductive hormone regimes mimicking those of the late Paleolithic.

Objective
The aim of this study was to determine whether a dietary intervention designed to Gluten free, low carb and increase intake of protein and vegetables, can reduces menopausal onset and symptoms in women.

Methods
We included 570 menopausal women, ages 40 to 79 years, at baseline who participated in the Dietary Modification and were not taking menopausal hormone therapy.
For each patient a medical record was compiled that collected personal and family history data, dietary habits, routine blood tests and ultrasound of the pelvic and abdominal organs, thyroid and breast every three months. Women who reported experiencing menopausal symptoms were compared with women not experiencing menopausal symptoms

Results
During the 4-year follow-up period, a Gluten free and low carb diet was associated to reducing menopausal symptoms, positive health effects on plasma lipid concentrations, in genitourinary system, in constipation and irritable colon, in skin, in cardiovascular functions, in hypertension, headache, back pain, in maintaining skeletal muscle mass and preventing sarcopenia and Weight loss

Conclusion
The climacteric syndrome can be interpreted as the result of a discrepancy between the recent lifestyle and reproductive patterns and the circumstances of life in the environment in which our ancestors evolved.

The climacteric syndrome

Hot flashes and perceived psychological stress. Assessment of the association in Colombian Caribbean women

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Context
Hot flashes (HF) are important and frequent menopausal symptoms, which are associated with decreased quality of life. There are few Latin American studies that value perceived psychological stress (PPE) according to the presence of HF, in women in a vital stage of climacteric.

Objective
To estimate the association between PPE and HF in a group of climacteric women of the Colombian Caribbean.

Methods
Cross-sectional study of the CAVIMEC project (quality of life in menopause and Colombian ethnic groups). Anonymous and voluntary participation, approved by the ethics committee of the University of Cartagena, Colombia. Two groups were formed: with HF (score greater than zero in the first question of the MRS) and without HF (score of zero). Quantitative variables are presented in Me [RI] and qualitative variables in%. The significance of the differences between groups was established according to homogeneity of the variance. Spearman's correlation coefficient was performed between HF (dependent variable) with the items and total score of the PSS-10 scales (independent variables) and unadjusted logistic regression was carried out between HF and the severity of PPE (according to PSS-10 average).

Patients
Women residing in various populations of the Colombian Caribbean.
Age 40-59 years, healthy, captured in their residences. Pregnant women and those with motor or cognitive disability were excluded.

Interventions
Sociodemographic characteristics form, Menopause Rating Scale (MRS) and Perceived Stress Scale (PSS-10) was applied.

Measurement of main results
HF and EPP.

Results
Study conducted in 471 women, 73 (15.4%) without HF and 398 (84.5%) with HF. No differences between the groups, in terms of age, BMI, diabetes, hypertension, coffee consumption, history of hysterectomy, ovarian preservation and use of hormonal therapy. Women with HF had more PPE than women without HF: 15.73 ± 5.33 vs. 19.12 ± 3.70, respectively, p <0.001. PPE was significantly and positively correlated with HF, rho = 0.2908 [95% CI: 0.2050 to 0.3714], p <0.0001, r2 = 0.0845. The items: being affected by something unexpected, being unable to control things in life and feeling nervous were also positively correlated, p <0.0001. High severity of PPE was factor associated with HF, OR: 4.55 [95% CI: 2.69-7.71], p = <0.05.

Conclusion
Significant statistical association was observed between EPP and HF.

The climacteric syndrome

Depression symptoms and thyroid status in euthyroid menopausal women

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Depression symptoms are a variety of disturbing complaints occurring during menopausal transition, many of which may be influenced by hormonal abnormalities other than related to sex steroids.
In this study, we investigated the associations between the intensity of depression symptoms measured with the Hamilton index and thyroid status measured with serum thyrotropin (TSH), and free thyroxine (fT4) in 202 euthyroid women admitted to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences because of climacteric symptoms.
The patients were both in peri- (74) and postmenopausal (128) state, with no thyroid disorders in their medical history. We obtained following results: age 54.2 +/- 4.9 years, BMI 26.8 +/- 4.6 kg/m^2, Kupperman index 26 +/- 13.1 scores, TSH 2.4+/-2.6 mU/l, fT4 1.2+/-0.37 ng/dl. In the total group we found a negative correlation between fT4 and the time since the last menses (R=-0.38; p=0.02). Results for depressive symptoms: in the total group, we demostrated positive correlations between TSH and weight loss (R=0.17; p=0.04), and between fT4 and: total value of Hamilton index (R=0.27; p=0.03), shallow sleep (R=0.31; p=0.02), waking early (R=0.28; p=0.03 and loss of interest in activities (R=0.27; p=0.03). In perimenopausal group, there was a positive correlation between fT4 and self-criticism (R=0,41; p=0,04). In postmenopausal group there was a negative correlation between TSH and symptoms of the genital system (R=-0,22; p=0.03) and positive correlations between ft4 and shallow sleep (R=0,33; p=0,04), waking early (R=0,44; p=0,008), loss of interest in activities (R=0,37; p=0,02), somatic symptoms of anxiety and fear (R=0,34; p=0,04), symptoms of the digestive tract (R=0,37; p=0,02) and symptoms of the genital system (R=0,37; p=0,02).
In conclusion, depression symptoms are related to thyroid status in euthyroid menopausal women.

The climacteric syndrome

May female temporomandibular dysfunction pain be a consequence of hypoestrogenism?

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The aim of this study was to evaluate temporomandibular dysfunction (TMD) in Climateric women: menopausal transition, early postmenopausal (up to 5 years of menopause) and late postmenopausal (over 5 years of menopause) women. Secondary we corrected the TMD with menopausal symptoms and Craniomandibular Index (MCI).

Methods - patients - intevention

The study was prospective and transversal coorte for evaluation menopausal complaints though Kupperman-Blatt index and TMD refers to a disorder that affects the temporomandibular joint and / or muscles associated with it (high female prevalence). Also, we collected data of sociodemographic aspects, such as education, income, marital status and ethnicity, as well as other variables related to TMD, such as MCI (which may influence our results).

Statistics

We used ANOVA test followed by Tukey test and Spearman Correctation test).

Main outcome measure

a) evaluate the influence of Kupperman index on the TMD and each period of climacteric is more prevalent.

Results

We found a correlation between the Blatt-Kupperman Index and the ICM (Spearman Correlation Test, $p = 0.0001$; $r = 0.4232$) and that in early postmenopausal women with longer study periods (> 4 years), both climacteric symptoms ($p = 0.02$) and TMD pain ($p = 0.02$) are significant. In addition, among the TMD Climacteric women, white women showed more climacteric complaints than those of other ethnic groups ($p = 0.008$). Also, education influences climacteric and TMD symptoms, especially in early postmenopausal women ($p=0.023$), In addition, two conditions indicates the possibility of one negatively influencing the other, exacerbating all symptoms of this period.

Conclusion

High Menopausal symptoms is correlated with worse TMD pain in cimacteric women, especially in early postmenopause.

The climacteric syndrome

Effect of two months oral intake of passion flower on menopause sleep disturbance: a triple blind randomized clinical trial

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Sleep disturbance rate is high during menopause and post menopause life (35-75%) and could cause anxiety, irritability, depression… It is suggested to manage it with safe methods for improving quality of life.

Objectives

To assess effect of two months intake of Passion flower on menopausal sleep disturbance.

Methods

In this triple blind randomized clinical trial, 80 volunteer healthy menopausal women (50-60 years), with sleep disturbance, whom had admitted in one of the clinics of Tehran University of Medical Sciences (TUMS), after filling in informed consent involved (Year 2015-2016). Tools had three main parts of demographic characteristics, Petersburg Sleep Quality Index (PSQI), Capsules intake chart. Participants randomly divided to two groups and received 2 grams Passion flower or 50 mg Starch oral Capsules as placebo in the same shape capsules, two times in a day for two months. Data analyzed by using SPSS 16. Study approved by ethics committee of TUMS:

Results

Equality of two groups was checked and there was no significand difference between personal characteristics and PSQI in two groups before intervention. In placebo group before intervention PSQI 10-15 was 70% and highest percent in passion flower group were 67.5% with PSQI 10-15 in the beginning of the study, 75% with PSQI 5-10 after one-month intervention, and 67.5% with PSQI less than 5 after two months intervention. The mean score of sleep disorders before intervention, after one-month intervention, and after two months intervention in Passion flower group were 11.3±2.1, 7.75±2.2 and 5.1±3.7, and in placebo group were 11.5±2.1, 9.1±2.2 and 5.15±2.8. Independent t test shows significant difference between two groups after one-month intervention (P>0.05), and Mann–Whitney U test showed significant difference after two months intervention (passion flower group PSQI was significantly less). Bonferroni test showed significant decrease and difference of sleep disturbance after one and two months (P>0.001)

Conclusion

Daily use of two-gram oral capsules of Passion flower showed significant effect on sleep disturbance after one month and after two months its effect was arisen. No side effect had been seen during intervention and after 6 months follow up. Its suggested to do other study with longer time intervention also comparing results with other Non pharmacologic methods for finding better results.
Acknowledgement: Granted by research department of TUMS, Year 2015-2018.

The climacteric syndrome

Association of postmenopausal time and menopausal symptoms with performance in exergame

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Objective

Associate postmenopausal time and menopausal symptoms with performance in exergame

Design

Cross-sectional study carried out at the Endocrine and Climacteric Gynecology Outpatient Clinic from November 2018 to May 2019 (Ethics Committee Approval 2,879,119 - Foment Number 201950226040). The study included 124 postmenopausal women (absence of menstruation for 12 months) under a convenience sample. A clinical and sociodemographic questionnaire containing the following variables was applied: sex, age, body mass index (BMI), schooling, post menopause time and marital status. All participants answered to health questionnaires validated in Brazil for evaluation of mood the Brunel Humor scale, Women's Health Questionnaire and Kupperman-Blatt Menopausal Index. After an interview, all the patients performed exergame activity - "MoviLetrando" (virtual reality game with movement activity measured by punctuation, number of correctness, number of errors, number of omissions, average touch time, average time of successes and time mean of errors), developed by the Laboratory for Research on Visual Applications of the State University of Santa Catarina (LARVA - UDESC) and presents independent scores for each movement activity. Participants were divided into two groups: early postmenopause (EP) andlate postmenopause (LP). Statistical analysis was performed using the SPSS software version 21.0 with homogeneity of the two groups by the Shapiro-Wilk test, Mann-Whitney test and Linear Regression Analysis for dependent variables.

Results

The women had a median age of 54 years (EP) and 60 years (LP), of which 37% (n = 46) were early postmenopausal women(EP) and 63% (n=78) were early postmenopausal women (LP). There was better performance among the early postmenopausal (LP) group compared to the late postmenopausal (LP) group, but they were not statistically significant. The regression analysis significant finding considering F (3, 121) = 3.37 and p=0.021. The age (β=-0.170, p=0.062), fatigue (β=0.188, p=0.058) and anxiety/fear (β=0.204, p=0.037) influenced the exergame score. The predictive capacity of the outcome was 5.6% (r2=0.056) in exergame score in postmenopausal women.

Conclusion

Age inversely influences exergame performance while fatigue, anxiety and fear directly influence exergame performance in postmenopausal women.

Surgery and interventional ultrasounds

Spontaneous acute intussusception in a pregnant woman: diagnostic traps

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Spontaneous acute intussusception in a pregnant woman: Diagnostic traps Radhouane ACHOUR, Nadia Lamiri; Mehdi FARHATI, Rim Ben Hmid Emergency department of Gynecology and Obstetrics of maternity and neonatology center Faculty of medicine of Tunis-El Manar University Tunis-Tunisia

Introduction

Acute intussusception in adults is rare and particularly so in pregnantwomen. Its incidence ranges from0.067% to 0.0015% (Choi et al., 2005). The non-specific presenting symptoms may be attributed to the pregnancy itself, making the diagnosis difficult. When it happens, however, it causes considerable morbidity and mortality for the pregnant woman and the fetus. In adults, such intussusceptions are mainly secondary to an intestinal disease and frequently a tumor.

Case report

We present the case of a A 21-year-old pregnant woman at nine weeks of gestation, gravida one para one, without medical history, was admitted with sudden start, permanent and paroxysmal pelvic pain two days prior to admission associatedwith rectorrhagia. She denied anymetrorrhagia, nausea, vomit, constipation or fever. The abdominopelvic ultrasound examination found an evolutive pregnancy at nine weeks of gestation with adnexal mass with ring of fire sign and a small amount of fluid in the cul-de-sac.
An emergency surgery was performed by laparoscopy. Histology of the resected bowel segment ileocecal intussusceptions without evidence of malignancy.

Conclusion

In summary, intussusception in pregnancy is a rare condition. The combined expertise of the obstetrician, radiologist, and surgeon are needed to manage the pregnant patient.

Surgery and interventional ultrasounds

Umbilical cord circumferences measurement as the predictor for neonatal birth weight

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Objective
To determine the association between umbilical cord circumference (UCC) and actual fetal weight.

Methods
This was a prospective study conducted in a tertiary university hospital between January 2018 till October 2018. Participants were obstetric patients planned for an elective caesarean delivery. The umbilical cord circumferences (UCC) were measured on the day of admission by a trained personal and estimated fetal weight was predicted using a formula utilizing the value from UCC findings. Subsequently, the actual fetal birthweight was recorded after the delivery of the baby.

Results
A total of 72 patients were recruited into the study. The mean UCC was 45.20+4.49mm. Male fetuses had larger UCC (45.57+3.78mm) as compared to female fetuses (44.86+5.10mm). The mean estimated fetal weight derived from a formula based on UCC was 3649+0.55kg. A larger measurement of UCC associated with heavier actual fetal weight. A cut off point of 50mm of UCC was associated with actual fetal weight of 4kg or more. The estimated fetal weight using UCC formula has higher specificity compared to conventional method with no significant difference in the actual fetal weight.

Conclusion
There was positive correlation between the UCC and the actual fetal weight. Hence, easy and quick sonographic assessment of the UCC may improve the prediction of fetal weight.

Surgery and interventional ultrasounds

Transvaginal ultrasound/sonovaginography vs magnetic resonance imaging: role in the evaluation of deep infiltrating endometriosis

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Context
Deep infiltrating endometriosis (DIE) refers to endometriotic implants that infiltrate pelvic peritoneum more than 5 mm. Transvaginal ultrasound complemented with sonovaginography (TVU/SVG) and magnetic resonance imaging (MRI) are the most commonly used methods for preoperative assessment, although there is not a consensus on the gold standard for the evaluation of DIE.

Objective
Compare the diagnostic performance of TVU/SVG and MRI in preoperative assessment of DIE, after correlation with surgical findings.

Methods
A restrospective study was carried in a diferentiated care center, evaluating the period between January 2010 and September 2019. We included the patients submitted to a laparoscopic surgery for suspicion of DIE, that have been previously assessed with TVU/SVG and/or MRI,

Results
A total of 72 women have been included, with a mean age of 34,9 ± 5,6 years. TVU/SVG and MRI were performed in 61 and 67 patients, respectively, with 53 women being submitted to both exams.
In the evaluation of the anterior compartment of the pelvis, TVU/SVG presented a sensibility of 42,8%, specificity of 92,6% and diagnostic accuracy (DA) of 86,9% (53/61). MRI presented a sensibility of 71,4%, specificity of 95,0% and DA of 92,5% (62/67). Regarding the posterior compartment of the pélvis, TVU/SVG presented a sensibility of 77,2%, specificity of 100% and DA of 78,7% (44/61). MRI presented a sensibility of 85,9%, specificity of 66,6% and DA of 85,1% (57/67). For the evaluation of uterosacral ligament lesions, TVU/SVG presented a sensibility of 10,4%, specificity of 87,5% and DA of 47,5% (29/61), while MRI presented a sensibility of 45,2%, specificity of 80,0% and DA of 58,2% (39/67).
For the evaluation of bowel involvement, that required a surgical procedure (shaving, discoid resection ou segmentary resection), TVU/SVG presented a sensibility of 57,5%, specificity of 57,1 and DA of 40,9% (25/61, while MRI presented a sensibility of 70,4%, specificity of 52,1% and DA of 64,2% (43/67).

Conclusion
When compared with TVU/SVG, MRI presented a higher diagnostic performance. For the evaluation of the whole posterior compartment, both exams presented diagnostic accuracies similar to those reported on literature. However, after an individualized analysis of the involvment of several structures of the posterior pelvis, both exams presented a reduction of their diagnostic performance.

Surgery and interventional ultrasounds

Estimation of fetal weight by clinical methods and ultrasound and correlating its accuracy with actual birth weight in term pregnancies; the CURFEW Study

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Objective

This study aims to determine if clinical formula using a Dare's formula is comparable to ultrasound in the estimation of fetal weight among women in term pregnancy.

Methods

This cross-sectional study was conducted among pregnant women at term (>37 weeks of gestation) at Sabah Women and Children's Hospital for a 12-month duration. All of these women underwent the fetal weight assessment one week before delivery. In cases who delivered later than a week, they will be excluded from this study. The clinical estimation of fetal weight was done using a clinical formula of the abdominal circumference (AC) x symphysio-fundal height (SFH); following the Dare's formula. Otherwise, the Hadlock's formula was used for the ultrasonography method (USG). The result was compared with the actual birth weight (ABW) to evaluate the accuracy between both methods further.

Results

A total of 257 women were included in this study with the mean age of 29.4±5.86 years. The mean gestational age was 39.1 ± 1.1 weeks, with 74% were multiparous. A total of 66.5% of patients had a vaginal delivery with the mean actual birth weight was 3133.7 ± 403.8 grams. The mean estimated weight by AC×SFH was 3760.1 ± 416.1 g and by ultrasound was 3035.89 ± 337.1g. The formula estimation method significantly overestimated the fetal weight. The mean errors for both clinical and ultrasound methods were 626.32g and -99.21g respectively $p<0.05$. The mean absolute percentage errors of both formula and ultrasound methods were 20.67% ± 11.62 and 7.86% ± 5.51 respectively $p<0.05$. Only 20.2% of formula estimation is within 10% actual birth weight compared to ultrasound 70.4%. The mean error was smaller for formula compared to ultrasound was 397.80 ± 320.82 and -434.4 ± 403.42 respectively. Otherwise, the mean absolute percentage error of formula estimation for the macrosomic fetus was smaller 9.61 ± 7.84, compared to ultrasound 12.07 ± 6.94. The accuracy of formula within 10% actual birth weight in macrosomia category was also better in formula estimation 60% compared to ultrasound 40%.

Conclusion

The ultrasound estimation of fetal weight is considered as a gold standard as compared to clinical estimation (Dare's Formula). Therefore, we suggest that supplementation with ultrasound is a must, should a crucial decision is required in a clinical situation to ensure a good fetal and maternal outcome.

Keywords: abdominal girth, symphysio-fundal height, Dare's formula, fetal weight, Hadlock formula

Surgery and interventional ultrasounds

Demographic and clinical characteristics of endometriotic patients undergoing multiple surgical treatment

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Evaluation of the demographic and clinical characteristics of endometriotic patients undergoing to multiple surgical treatment.

Patients

A total 218 patients were divided into two group. One group was patients with primary surgery (n=150) while the another group was patients with multiple surgeries (n=68).

Methods

A total of 218 patients reproductive age (25-45 years old) with previous histological diagnosis of endometriosis after one or multiple surgeries were included from four hospitals (2 in Italy, 2 in China) in this observational cross-sectional study. A structured questionnaire was administered to these patients after surgical treatment. Statistically significant differences between groups were determined using Mann-Whitney U test and Chi-square test or Fisher's exact test.

Results

The median age at the time of first diagnosis of endometriosis was younger in patients with multiple surgeries. Patients with multiple surgeries had more dyspareunia (47.5% versus 29.7%, p=0.025) and non menstrual pelvic pain (52.4% versus 41.4%, p=0.028) after surgery when compared to the patients with primary surgery. More individuals with primary surgery tried pregnancy after surgery (38.3% versus 35.4%, p=0.011) and were more likely to conceive (34.9% versus 22.6%, p=0.004) when compared to the patients with multiple surgeries. The type of surgery (laparoscopy or laparotomy), the subtype of endometriosis, the type of intervention, previous treatment before surgery and postoperative medication showed no difference between two groups.

Conclusions

Patients who underwent multiple surgical treatment were younger, more troubled by infertility, and more susceptible to pain after operation.

Surgery and interventional ultrasounds

Laser treatment of female urinary incontinence and genitourinary syndrome of menopause – an update

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Context
Noninvasive treatment is recommended as first line for urinary incontinence (UI) in women. However, surgical procedures are more likely to be implemented to cure UI but are associated with more adverse events.

Objective
Less invasive operative mesh techniques are relatively effective, but not immune to complications such as bleeding, bladder perforation, urethral injury, infection, and the retention requiring mesh resection. In patients for whom the risks of anesthesia and surgery are too high, a minimally invasive approach is recommended and further research is needed in terms of more compliant, less invasive and low-cost methods for the treatment of stress UI and pelvic floor dysfunction.
Contemporary scientific and technological breakthroughs have led to better clinical outcomes with minimally invasive procedures with shorter recovery times and lower implicated costs. In this sense, recent evidence supports laser treatment as an effective and compliant intervention for stress UI.

Methods
A non-systematic review of the literature was derived from PubMed database up to March 2019. Keywords "laser" and "urinary incontinence" yield 370 articles. After exclusion for incontinence in male, laser use in surgery, non-laser techniques and review articles, 24 papers met criteria regarding laser use in women with urinary incontinence.

Results
Laser effect in SUI patients was the primary goal in 21 studies, OAB in 1, GSM in 1 and histology in 1 study. A total of 1,452 patients were enrolled at the 1-36 months follow up (mean 7.04 months). In average 1.9 laser sessions per patient, an average reduction in ICIQ-UI SF scores was 5.9, an average 1-hour pad test reduction was 16 grams with an average continence rate after laser treatment of 44.5%. Future studies need to be designed taking mentioned considerations into account, including the histological assessment performed immediately after treatment that will help compare morphology at baseline with changes in the vaginal architecture following laser procedure. Next studies should focus on the individual patient level in order to predict personal risk or benefit based on the decision of undergoing a given proposed procedure. Simultaneously, predictive systems may impact public health policies in terms of prevention.

Conclusions
In spite of promissing results, there is still need for long term consistent evidence analyzing laser efficacy and safety in the treatment of female UI.

Surgery and interventional ultrasounds

Vitamin D deficiency as a significant associated factor in pelvic floor disorder in Slovenian women

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Objective
Vitamin D is vital for skeletal integrity as well as optimal muscle work. Its deficiency cause athrophy of muscle fibers type II, clinically shown as muscle fatigue and lower muscle work. High incidency and prevalence of vitamin D deficiency as well as pelvic floor disorder is found in postmenopausal women rising the question whether the entities could be connected.

Methods
We enrolled 50 patients of postmenopausal age with pelvic floor disorder (descensus, prolapse, stress urinary incontinence) and 48 age and weight matched women without pelvic floor disorder. The clinical confirmation of disorder was POP-Q test at gynaecological examination. Each participant fulfilled the questionaire and gave blood sample for 25-OH-vitamin D determination.

Results
Groups didn't differ significantly in body mass index, neither parity, nor 25-OH-vitamin D concentrations. However, significantly higher incidence of vitamin D deficiency (25-OH-vitamin D < 50 nmol/l) was found in the test group according to controls. Higher prevalence of caesarean section were were found in the control group. Being comparable in actual free-time physical activity, groups importantly differ in the pattern of physical activity in the proffesion.

Conclusions
Vitamin D deficiency is an accountable factor connected to pelvic floor stability in Slovenian women, next to specifics of physical activity in proffesion and vaginal deliveries. Determination of vitamin D in postmenopause and replenishing possible deficiency is important for women's health.

Surgery and interventional ultrasounds

Role of cerebroplacental ratio in prediction of adverse perinatal outcome in term pregnancies

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Objective
Prediction of intrapartum fetal compromise and neonatal intensive care unit admission (NICU) by the cerebroplacental ratio in term pregnancies.

Methods
601 patients with singleton, term (37-40 weeks) pregnancy were recruited in a prospective observational study conducted from June 2017 to June 2019.

Patient interventions
Ultrasound was done for fetal biometry, umbilical artery (UA) and middle Cerebral Artery (MCA) doppler parameters. Intrapartum variables and neonatal data were recorded, including CTG abnormalities, mode of delivery, birthweight, Apgar score and admission to NICU.

Main outcome measures
The main outcome in this study was operative delivery including both caesarean and instrumental vaginal delivery for presumed fetal compromise. The second outcome was need for admission to the neonatal intensive care unit (NICU).

Results
Multivariate logistic regression analysis was done to see the association of various variables with the need for operative delivery and it showed that UA PI MoM(p=0.001), MCA PI MoM (P=0.001) and CPR MoM (P=0.001) were significantly and independently associated with operative delivery for fetal compromise. Multivariate logistic regression analysis was also done to see the association between various variables and need for NICU admission and it showed that UA PI MoM(p=0.004), MCA PI MoM (0.009), and CPR MoM (P=0.003) were also significantly and independently associated with NICU admission. When patients were divided into 4 groups according to a combination of a BW cutoff of 10th centile and a CPR cutoff of 0.6765 MoM it was observed that rates of operative delivery for fetal compromise was higher for AGA with low CPR compared to SGA with normal CPR MoM (43.1%,37.5% respectively) while rate of NICU admission was higher among SGA with normal CPR compared to AGA with low CPR(37.5%,27.58% respectively). Hence birthweight seems more predictive for the need for NICU admission and abnormal CPR is a better predictor for the need of operative delivery for fetal compromise

Conclusion
Lower fetal mean CPR and CPR MoM were independently associated with the need for operative delivery for presumed fetal compromise and with NICU admission at term. Rate of operative delivery for presumed fetal compromise was higher in AGA fetuses with low CPR than in SGA fetuses with normal CPR (43.1% and 37.5% respectively) indicating that CPR is more strongly associated with fetal compromise due to placental insufficiency than is BW

Surgery and interventional ultrasounds

Ultrasound features and marker levels of hormonally active ovarian tumors

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Subjective ultrosonographic assessment is currently considered to be the best method of differentiation between various types of ovarian tumors. The aim of this study was to evaluate chosen ultrasonographic features and CA125 levels of hormonally active ovarian tumors.

Patients

1135 women with ovarian tumor were diagnosed between 2006 and 2014 in the Division of Gynecological Surgery Poznan University of Medical Sciences.

Methods

Tumors were evaluated in the ultrasonography examination according to criteria: 1) the structure of the tumor 2) volume of the tumor 3) vascular features 4) structure of internal wall. The evaluation of the CA125 level was also carried out.

Results

There were 60 hormone-secreting ovarian tumors, including: 20 granulosa cell tumors, 28 fibrothecomas, 10 dysgerminomas and 2 struma ovary. The study group also included 9 metastatic ovarian tumors. Granulosa cell tumors occurred most frequently as large unilocular-solid cyst, moderately to highly vascularized and the vascularization has low-resistant flow. Dysgerminomas were predominantly large unilocular-solid cyst or purely solid tumor, with minimal to moderate low-resistant vascularization. Fibrothecomas were solid mass with minimal, high-resistant vascularization. Struma ovarii occurred as a small, solid mass with very abundant, high-resistant vascularization. Metastatic ovarian tumors presented
mainly as a multilocular-solid tumors with strong, low-resistant vascularization. Papillary projections were most frequently observed in metastatic tumors and granulosa cell tumors in 56% and 50% respectively, although only half of granulosa cell tumors papillary projections were bigger than 3mm. Elevated CA125 levels were found only in the case of metastatic ovarian tumors.

Conclusion

Hormonally active ovarian tumors present several ultrasonographic features which may facilitate preoperative diagnosis.

Surgery and interventional ultrasounds

Non ablative erbium laser treatment for female stress urinary incontinence

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Background
Stress urinary incontinence (SUI) is a common cause of urinary incontinence and is affecting large number of women influencing significantly their quality of life. There is a large range of therapies for SUI from lifestyle/behavioral modification to surgical interventions, and these therapies differ in terms of both effectiveness and risk. However, current treatment options raised some concerns regarding safety and efficacy and there was a quest for new treatment options. Several years ago vaginal laser therapy was offered as a minimally invasive treatment option for SUI.
The purpose of this study was to evaluate long term efficacy and safety of erbium laser treatment for female stress urinary incontinence (SUI).

Methods
In this single center prospective study in the period from April 2014 to January 2016 we performed ErYAG laser thermo-therapy on a number of female patients having SUI. ICIQ-UI as well as ISI by Klovning were used for assessment of SUI. Patients received two laser sessions with 4-6 weeks interval. Patients' satisfaction was measured with 10 point numerical scale. Follow-ups were performed at 1, 3, 12 and 18 months. Long term follow-ups were performed via telephone interviews during which aside of ICIQ-UI and patients' satisfaction additional questionnaire was used to assess the duration of SUI improvement and patients' readiness to repeat the treatment. Adverse events were registered at every follow-up.

Results
132 patients with SUI were included in this study. Average age was 50.3 yrs (range 23-75) and parity 1.9 (range 0-4). Average score on ICIQ-UI before the treatment was 11.8 and at the 3 months FU 3.7, (improvement of 8.1 point). At 3 months FU 39.2% of patients were dry and 96.9% of patients improved their ICIQ score. All reported adverse effects were mild and transient. 75% of patients have the full effect lasting at least 12 months and 24% at least 18 months. Average duration of full effect was 13.0 months. 85% of patients were not disappointed when the symptoms started to come back. 97% of patients was satisfied with treatment (average score at 18 months was 7.9/10; 68% with grades 8-10 and 41% with 10/10). 98% of patients would repeat the therapy.

Conclusions
Erbium laser treatment showed efficacy in improvement of female SUI with no major adverse effects noted. Patients' discomfort during the treatment was minimal and satisfaction very high.

Surgery and interventional ultrasounds

Can lasers reduce overactive bladder symptoms?

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Objective

The purpose of this lecture is to report about studies in which new laser treatment was used for therapy of overactive bladder (OAB) symptoms

Methods

In last few years four clinical studies were published in which the authors were assessing the efficacy and safety of non-ablative Erbium YAG laser for the treatment of the overactive bladder symptoms. In all of these studies the OABSS score was used as a measurement tool for efficacy. In two studies the comparison of laser treatment with surgery and with standard medications (anticholinergics and beta 3 adrenoceptor agonists) were performed. Patients received between one and three laser treatment sessions (one session in Tien study, two sessions on Lin study and three sessions in Okui studies) and were follow up between 3 months and 1 year. Adverse effects were observed at every follow-up and in one of the studies patients were interviewed about their satisfaction with the results.

Results

In all four studies 165 (35, 30, 50, 50) female patients were treated with non-ablative ErYAG laser and in two studies with comparison to surgery and medicaments additional 100 patients were included in control groups. Patients were assessed with OABSS questionnaire. The OABSS scores significantly improved in all four studies (from 8.16 to 3.76; from 4.1 to 2.7; from 8.2 to 6.1). At 6 months follow up the improvement of symptoms in the laser groups was still significant. The adverse effects were all mild and transient. Majority of interviewed patients were satisfied with the treatment and the outcome.

Conclusions

Non-ablative ErYAG laser therapy for overactive bladder (OAB) symptoms demonstrated significant improvement of the OABSS score. This laser therapy seems to be a promising option for OAB patients not willing to perform long term medication therapy. However more studies with larger number of patients and longer follow-up are needed for better understanding and stronger evidence of this new treatment option.

Surgery and interventional ultrasounds

Safety of energy based devices for genitourinary syndrome of menopause and stress urinary incontinence

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Objective

Non-surgical use of energy based devices (EBD) in gynecology is one of the fastest growing segments in the EBD market offering protocols for wide range of indications like are vaginal urinary incontinence, genitourinary syndrome of menopause, pelvic organ prolapses, vaginal laxity, lichen sclerosus and others. In spite of many clinical studies executed and published, showing good results and very low level of adverse effects, there are still a lot of doubts and criticism considering clinical evidence of efficacy and safety of these treatments. In this paper we are analyzing the safety of EDB for gynecological applications.

Methods

Energy based devices used for gynecology are mostly lasers and radiofrequency devices, but there are also a few high intensity ultrasound devices present on this market. We analyzed the mechanisms of action of these three types of EBD, claimed depths of penetration and range of medical indications. An overview of EBD and published clinical studies is given with reported adverse effects. Also, a worldwide survey among the users of non-ablative erbium laser technology was conducted with the aim to establish the safety and efficacy of intra-vaginal use of this technology. The questionnaires asking about the number of patients treated, the adverse effects registered and the level of patients satisfactions with the treatments outcomes were distributed to the large number of users.

Results

More than 40 different EBD were identified to offer gynecological applications. Just two of them have a large base of published clinical studies, next 5-6 EBD have a few clinical studies done and published, while the large majority so far doesn't have any clinical validation of their technology. Data from the published studies showed that there were no serious adverse effects reported. Also, the preliminary results of the still on-going survey of non-ablative erbium intra-vaginal laser are showing very low number of adverse effects reported and all of the reported adverse effects were mild and temporary.

Conclusions

The most of the EBD used for gynecology don't have clinically validated safety of their devices, however a two of them, being on the market for almost ten years and having large body of evidence in many published studies are showing very high safety profile and also very good efficacy in selected indications.

Surgery and interventional ultrasounds

Outcome in women undergoing uterine artery embolization for arterio-venous malformation following pregnancy

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Objective

To analyse the outcome of patients with symptomatic arterio-venous malformation(AVM), post pregnancy, managed conservatively by uterine artery embolization(UAE).

Method

From July 2017 to December 2019, 15 patients presented with abnormal uterine bleeding following pregnancy, diagnosed as AVM and managed with UAE. Their follow up period ranged from 6 to 30 months. Medical records were reviewed for the indication of UAE, presenting symptoms, post UAE complications and subsequent fertility. Trans-Vaginal Sonography with doppler made the initial diagnosis and confirmed with angiography at the time of UAE.

Results

The mean age was 28.4±3.82 years and mean parity was 1.3. Out of 15 cases, 9(60%) presented after abortion, 2 of these were after second trimester abortion. Medical abortion was seen in 6, surgical evacuation in 2 and spontaneous abortion in 1 patient. Among all abortions, 8/9(88.8%) underwent D&C for retained products of conception(RPOC). 2 patient had LSCS and 4 patients(22.3%) had normal vaginal delivery and 2 patients among them presented with secondary Postpartum hemorrhage(PPH) for which they underwent D&C for RPOC. 9/15(60%) patients presented with continuous BPV post abortion or delivery and 6/15(40%) patients had irregular but heavy bleeding. Mean duration of symptoms was 91±85.7 (30-360) days. Bleeding was controlled in all patients with a mean duration of 3.6±0.97(3-6) days after UAE except for 1 patient who required repeat UAE one month later. Embolic agents used for UAE was PVA particles(300-500µm diameter) in 2(13.3%) patients, 30%glue injection in 3(20%) patients, combination of PVA with glue injection in 4(26.6%) and PVA with gelfoam in 6(40%) patients. All resumed normal menstrual cycle in 31.3±5.2(24-42) days. On subsequent follow up 8/15(53.3%) patients developed abnormal vaginal bleeding. 10/15(66.7%) patients desired conception, of whom 5(50%) conceived within mean duration of 13.2±5.1(6-19) months after UAE. Two women carried pregnancy till term and one had preterm caesarean section in view of small for gestation age with oligohydraminos, also had PPH which was managed medically. Other 2 patient who got pregnant, 1 had spontaneous abortion at 6 weeks of gestation and other is 13 weeks pregnant at present.

Conclusion

UAE for management of symptomatic AVMs post pregnancy is an attractive treatment modality. It gave symptomatic relief in majority of women and did not impair fertility.

MAP: the infertile couple, ovulation induction and donation

Fertility in women with congenital malformations of the cervix

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Introduction

Congenital malformations of the cervix are caused by abnormal development of Mullerian system, they may arise as a result of abnormal fusion of the mullerian ducts with the urogenital sinus, imperfect canalization of the lower mullerian system, or segmental atrophy of a normally formed mullerian system.

Case report

We report a case of a congenital cervical atresia diagnosed at the age of 28 years. Aged 32 years was referred to our unit and had a successful pregnancy after *in vitro* fertilization.

Conclusion

Infertility is a common complication and the malformation generally require reconstruction or disobjection of the outflow tract. However a successful pregnancy outcome can be achieved in women with congenital cervical abnormalities.

MAP: the infertile couple, ovulation induction and donation

Uterine microbiome and chronic endometritis in repeated IVF failure

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For near a century there was a strong opinion that healthy uterine cavity is sterile. During last several decades it was proved that uterus in healthy women is characterized by a large diversity of microorganisms, mostly presented by Lactobacilli. Moreover, women with different gynecological pathologies have more pronounced variety of microorganisms. The objective of the study was to compare the endometrial microbiota in women with repeated IVF failures with and without chronic endometritis (CE). Endometrial biopsy was performed in 22 women with two or more unsuccessful IVF attempts from 22 to 24 day of menstrual cycle using Pipel catheter and catheter for intrauterine insemination to avoid contamination by vaginal and cervical microbiota. Immunohistochemical analysis to determine Syndecan-1 (CD138) positive cells and next-generation sequencing of the 16S ribosomal RNA gene were performed. CE was diagnosed if plasma-cell density was above the 95th percentile. 15 women met the diagnostic criterion of CE. 7 women were CE-negative (31.8%). The most abundant detected bacteria belonged to the phyla: Furmicutes, Proteobacteria, Actinobacteria and Bacteroidetes. All CE-negative women (31.8%) had median relative abundance of Lactobacillus of 94.12% in uterine microbiome, whereas CE-positive women (68.2%) – of 0.42%. It is important to note, that all CE-negative women had to undergo IVF procedure due to male infertility factor and didn't have any serious gynecological disorders (chronic endometritis, endometrial polyps, low endometrial thickness). In group of CE-positive women 22 types of different bacteria genus also were detected, including genus of Staphylococcus, Acinetobacter, Streptococcus, Gardnerella, Ralstonia, Cutibacterium and others. Median relative abundance of Staphylococcus was 32.4%, Acinetobacter - 23.7%, Streptococcus 19.4%, Gardnerella - 25.7%, Ralstonia 9.8%, Cutibacterium 7.6%. Conclusion: CE is associated with high microbiological diversity of endometrial fluid and can be a reason of repeated IVF failures. Rationalizing antimicrobial therapy of women before IVF protocols taking into account the data about presence or absence of CE markers can improve the outcomes of IVF attempts.

MAP: the infertile couple, ovulation induction and donation

Letrozole versus clomiphene citrate: which is better for ovulation induction?

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Context
Ovulation induction is one of the possible infertility treatments for patients with Polycystic Ovarian Syndrome (PCOS), mild endometriosis and Infertility without an apparent cause (IWAC). For many years, ovulation induction was performed mainly with Clomiphene Citrate (CC), especially in patients with PCOS. However, with the introduction of Letrozole (LTZ), similar results have been obtained in the ovulation rate.

Objective
To evaluate the ovulation response in patients with PCOS, mild endometriosis and IWAC submitted to LTZ or CC induction

Methods
An observational retrospective cohort study at HSL/PUCRS, Brazil, from April 2018 to April 2019. Ovulation control was performed by serial ultrasound. Data were obtained through medical records analysis. For ovulation induction CC 50-100mg/day or LTZ 2.5-5mg/day was used, plus gonadotropins when indicated. A total of 48 patients were evaluated, including 128 cycles. Patients with PCOS, IWAC and mild endometriosis, without associated male factor, were included. All patients had patent tubes, except two patients with one tube obstructed. In the sample, there were 3 patients with hypothyroidism (2 of them with PCOS and 1 with IWAC). Two patients and 3 cycles were excluded due to the presence of both endometriosis and PCOS.

Results
128 complete cycles from 48 patients diagnosed with PCOS, endometriosis and IWAC were analysed - median 2 [1-3.75 cycles/patient]. Ovulation was observed in 85% of cycles and 95% of patients in at least 1 cycle. Mean age from women and men were 33.5±4.6 and 36.2±7.9 years, respectively. The women body mass index was 26.0±4.2 kg/m^2 (minimun 19.2 - maximum 41.5). When comparing the ovulation percentage per cycle (without medication, n=43 vs. CC, n=55 vs. LTZ, n=30), the following results were found, respectively: PCOS (50%; 71%; 77%, P=0.50); endometriosis (91%; 86%; 93%, P=0.80), IWAC (81%; 88%; 100%; P=0.88). There was no difference in corpus luteum number when CC was compared to LTZ.

Conclusion
There seems to be no ovulation induction benefit for more than 6 cycles in infertility patients. For many years, drug of choice has been CC. However, this concept has been changing, making room for the use of LTZ, especially in PCOS patients, which is already considered by many authors a drug of choice in this pathology. LTZ and CC in PCOS and endometriosis patients had similar response on ovulation induction, however, seems to have a tendency for better results with LTZ.

MAP: the infertile couple, ovulation induction and donation

Results of the use of HCG, agonist GnRH and dual trigger on *in vitro* fertilization and evaluation of risk factors for suboptimal maturation rate

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Context
The final process of ovarian hyperstimulation is oocyte maturation and has a direct influence on the results of *in vitro* fertilization (IVF). The trigger used as standard is hCG, and for patients, at risk of OHSS, the agonist GnRH. Dual trigger seems to be the best option for poor ovarian responders, with better oocyte maturation rates, and higher pregnancy rates. We still do not have a clear comparison between the three triggers and their results that evaluate oocyte maturation rates; seeking the clinical decision to the best IVF result, offering a better indication with less risk, and thus personalizing the treatment of each woman.

Objectives
Compare oocyte maturation rate in the treatment of IVF / ICSI between the use of hCG, agonist GnRH and dual trigger, and evaluate the associated risk factors, which led the women to present sub optimal maturation rates

Methods
Retrospective observational cohort study.

Patients
A total of 856 women submitted to IVF who performed the oocyte retrieval, were classified into three groups according to the type of trigger used: 1- hCG; 2- GnRH agonist and 3- dual trigger.

Interventions
None. Main outcomes Measures: Primary outcome was oocyte maturation rate, secondary outcomes are pregnancy rate per oocyte retrieval and risk factors for low oocyte maturation rate.

Results
Average age was 35.9 ± 4.6 years. Maturation rate was 77% (group 1); 76% (group 2) and 83% (group 3) ($p = 0.0035$). Group 2 showed women with better ovarian reserve, greater number of oocytes collected, mature oocytes and embryos in relation to the other groups ($p < 0.001$). Cumulative clinical pregnancy rate was 42.54% (group 1); 41.78% (group 2) and 47.05% (group 3) ($p = 0.755$). Abortion rate was 8.57% (group 1); 12.44% (group 2) and 11.76% (group 3) ($p = 0.648$). The null maturation rate was 3.03% and the maturation rate <70% was 28.18%. Low ovarian reserve and low doses of FSH administered during the ovarian stimulation were associated with a higher chance of null maturation rate.

Conclusion
The different types of triggers do not influence the results of IVF cycles. Low ovarian reserve is associated with higher chance of null maturation rate.

MAP: the infertile couple, ovulation induction and donation

Pregnancy outcomes in one follicle-one oocyte IVF/ICSI cycles

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Context
A higher oocyte number obtained from IVF/ICSI is associated with a higher live birth rate. However, there is a paucity of data on pregnancy outcome following retrieval of a single oocyte.

Objectives
The primary aim was to investigate pregnancy outcome following retrieval of a single oocyte from a single follicle during a COH IVF/ICSI cycle. The secondary outcome was to compare whether the pregnancy outcomes differ if a single oocyte was retrieved from women with two and three >15mm follicles.

Methods
This retrospective study included women undergoing fresh IVF/ICSI cycles between 2015 and 2019 who had only one oocyte retrieved. Data were collated from the Unit's database and cross-referenced with paper records. Cycles were categorised based on the number of dominant follicles >15mm present on TV scan on the day of ovulation trigger, when the solitary or lead follicle was >17mm. Statistical analysis was performed using chi-square test for categorical variables.

Patient(s)
Women were aged between 27 and 44 at a BMI 19-32 kg/m^2 with primary or secondary infertility and undergoing IVF/ICSI treatment.

Main outcome measure(s)
Clinical, embryological and pregnancy outcome data were collated.

Results
During the study period, in 80 cycles only a single oocyte was retrieved. Two of these cycles were excluded from the analysis due to incomplete information or oocyte donation. Of the remaining 78 cycles, 51 had a single follicle, 15 had two and 12 had three follicles. The live birth rate (LBR) per oocyte retrieval (OR) was significantly higher in patients with two follicles compared to one follicle (26.7% [4/15] vs 7.8% [4/51], $p<0.05$). With two pregnancies ongoing from the single follicle group LBR could be uplifted to 11.8% (6/51). There was a similar trend in the clinical pregnancy rate (CPR) per OR and per embryo transfer (ET): with two follicles, the CPR/OR was 33.3% (5/15) and for a single follicle 11.8% (6/51). CPR/ET was 41.7% (5/12) with two follicles compared to 20% (6/30) with one follicle (both $p<0.05$). In women with a single oocyte collected from three stimulated follicles, the LBR and CPR/OR were identical at 16.7% (2/12) and the CPR/ET was 25% (2/8).

Conclusions
Livebirth and clinical pregnancy rates in women with a solitary follicle during IVF/ICSI treatment were higher than expected. Women should be given the choice to proceed with oocyte retrieval in the presence of one mature follicle rather than cancelling the cycle.

MAP: the infertile couple, ovulation induction and donation

Using progestin in controlled ovarian stimulation: a comparison of IVF outcomes between follicular and luteal stimulations

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Context
Multiple follicular recruitment waves in association with new techniques for freezing oocyte and embryos provide new opportunities for reproductive physicians to develop new protocols of ovarian stimulation. Increasing attention has been given to the use of progesterone for pituitary suppression, in both, follicular and luteal phases. However, there is no consensus about the effect of this new flexible approach to ovarian stimulation in IVF outcomes.

Objective
To compare the use of progestin in follicular and luteal phase stimulation for IVF outcomes.

Patient(s)
For this retrospective cohort study, data from 100 ovarian stimulation cycles conducted in a private IVF center, between Jan-Dec/2018 were collected and divided according to the phase of stimulation: Follicular phase (FP, n=39), initiated on day 2 of the menstrual cycle, and Luteal phase (LP, n=61), started after LH peak.

Methods
Patients received gonadotropins and progestin, respectively for follicular recruitment and pituitary suppression. Oocyte retrieved was performed 35h after trigger. Laboratorial procedures were conducted according to standard practice. All embryos were cryopreserved for a later transfer. Primary outcomes: cycle cancelation, stimulus duration and total gonadotropin administrated. Secondary outcomes: oocyte yields obtained, rate of MII and blastulation (number of blastocyst/number of zygotes). R software 3.5.1 was used for data analysis. Categorical variables were presented % (Chi-squared). Continuous variables were presented as mean±SD (independent t-test). An α of 5% was adopted.

Result(s)
There were no differences between groups regarding to cycle cancelation (FP: 10.3% vc LP: 9.8%; p>0,999). However, stimulus duration was higher in the LP group (FP:11.3±1.9 vs LP: 12.2±2.3; p=0,041), as well total dose of gonadotropin administrated (FP: 2233.2±845.4 vs 2718.5±618.4; p=0,001). Regarding secondary outcomes, number of oocytes and rate of oocyte maturity were similar between groups (FP: 7.9±5.7 vs LP: 9.6±6.7; p=0.218) and (FP: 80.6±22.8 vs LP: 84.4±14.4; p=0.739), respectively. Blastulation rate was higher in the LP (35.7%) compared to the FP group (24.2%), p=0.046.

Conclusion
Although higher gonadotropin administrated and stimulus duration, LP stimulation with progestin provides improved blastulation. Our finding may be an indication that oocytes from the second follicular wave could acquire better competence when using this particular stimulus protocol.

MAP and fertility preservation

The impact of cerebrolysin on poor responders

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Introduction

Poor ovarian response (POR) often means low success rates after *in vitro* fertilization (IVF). It has been recognized that neurotrophins know for their role in neuronal survival involved in the maturation of the ovarian follicle. These neurotrophins include nerve growth factor(NGF), brain derived neurotropic factor(BDNF), neurotrophin 4/5 (NGF), and neurotrophin 3 (NT-3) have been identified in the mammalian ovary. Cerebrolysin is a neurotrophic and protective similar to NGF that acts as antioxidant and protect neurons form ischemia and hypoxia.

Material and Methods

A total of 30 patients with a history of poor ovarian response undergoing IVF cycle divided into 2 groups, Group1: 15 cases taking cerebrolysin 5mg daily for 2 months. Group 2:15 cases not taking any treatment as control. It is a prospective cohort study, oocyte and embryo number and quality were recorded before and after treatment.

Results

Statistically significant increase in oocyte and embryo number and quality before and after treatment in the group taking cerebrolysin compared to control with p-value<0.05.

Conclusion

Cerebrolysin treatment resulted in high number of oocyte retrieval, oocyte fertilized embryo overall and of grade -1 embryo, this help in increasing pregnancy rate in poor responders.

MAP and fertility preservation

Development of a hydrogel from decellularized bovine ovarian tissue for a transplantable artificial ovary

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Context

The transplantable artificial ovary (TAO) is an experimental fertility restoration strategy for women who cannot undergo ovarian tissue transplantation due to the risk of reintroducing malignant cells. One major requirement for the TAO is creation of a biomimetic 3D matrix to encapsulate isolated ovarian follicles and cells.

Objective

Our goal was to develop a hydrogel based on decellularized bovine ovarian extracellular matrix (boECM) to support survival of isolated mouse preantral follicles.

Experimental methods

Bovine ovarian tissue was decellularized using two different protocols. Freeze-dried tissue was lyophilized and pepsin-digested to develop two hydrogels, boECM1 and boECM2. Cow ovarian tissue (n=3), boECM1 (n=3) and boECM2 (n=3) hydrogels were compared to determine decellularization efficiency by quantifying dsDNA (Quant-iT™ PicoGreen). ECM preservation was evaluated by measuring collagen and glycosaminoglycan (GAG) content using hydroxyproline and 1,9-dimethyl-methylene blue respectively. Hydrogel rigidity was assessed by rheology. Mouse preantral follicles (n=339) were isolated from mouse ovaries (n=6) and *in vitro*-cultured in both hydrogels. Seven days later, they were investigated for viability (live/dead assays) and growth (follicle diameter).

Results

dsDNA was significantly higher ($p<0.0001$) in native tissue than in boECM1 or boECM2. A significantly greater reduction in dsDNA was found in boECM2 compared to boECM1. Collagen represented 67.3±29%, 89.5±5.8% and 78.1±17.1% of the dry weight of native tissue, boECM1 and boECM2 respectively, with no difference between groups. GAGs were significantly more abundant ($p<0.01$) in native tissue than in boECM1, but there was no difference with boECM2, which was also stiffer ($p<0.0001$) than boECM1. On day 7 of *in vitro* culture, there was no difference in follicle recovery, viability or growth between the two hydrogels.

Conclusions

We developed two different hydrogels from decellularized cow ovary, with boECM2 showing lower levels of dsDNA, more GAGs and greater rigidity than boECM1. Since no differences were seen in terms of hydrogel biocompatibility upon mouse follicle culture, we propose boECM2 as a promising new biomimetic scaffold for human application. Further studies with human follicles are nevertheless needed to assess boECM2 efficacy.

MAP and fertility preservation

Optimization of the laboratory protocol for the ovarian tissue cryopreservation

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Context

Fertility preservation includes a set of procedures aimed to preserve the reproductive potential in women at high risk of losing ovarian function (chemotherapy, radiotherapy, and some benign conditions associated with a high risk of POF). Cryopreservation of oocytes is currently the eligible method for most patients. An alternative approach, still considered experimental, is represented by ovarian tissue cryopreservation (OTC) which shows the following characteristics: 1) it is the only option for prepubertal girls; 2) also endocrine ovarian function is preserved; 3) controlled ovarian stimulation is avoided; 4) it allows spontaneous pregnancies. To date, over 130 children have been born after OTC and transplantation – only two in Italy - but only a few centres are able to offer it in the clinical routine and a standardization of the procedure is required.

Objective

1) To compare two protocols (P1, P2) of slow freezing for the ovarian cortex; 2) To optimize and validate the protocol to be applied in the clinical practice.

Methods

Tissue integrity before and after cryopreservation/thawing was assessed by optical microscopy (MO) and by transmission electron microscopy (TEM).

Patients/samples

The comparison between P1 and P2 was performed using both human (collected during during laparoscopic procedures for benign ovarian disease) and bovine ovarian cortex samples. Bovine ovaries (n = 15) were also used to acquire manual skills for the isolation of the ovarian cortex. The laboratory protocol optimization and validation was carried out using only human ovarian cortex (n = 20), recovered during laparoscopic surgery.

Main outcome measures

The conservation status of the tissues using a scoring system (ranging from 1 to 5) for grading the integrity of both stroma and follicles.

Results

P2 showed a greater efficacy and was therefore selected for the protocol optimization phase on human ovarian cortex, which represent our learning curve for OTC, reaching a plateau with high score (optimal integrity of stroma and follicles) for the last 7 human samples.

Conclusions

This study has been of fundamental importance before introducing otc as a new strategy for female fertility preservation. The final step of validation is ongoing. Given the limited number of cases, this activity should be centralized in few highly specialized laboratories in order ensure the safety, efficacy and quality of the procedure, in line with the international standards.

MAP and fertility preservation

Fertility among older women in Tunisia

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Introduction

It is thanks to the development of assisted procreation techniques (ART) that the participants were able to meet the growing demand and the strong desire to have children, women aged 38 and over. In natural cycle, there is a physiological decrease in female fertility potential with advanced age. In addition, in this case; pregnancy is associated with increased rate of spontaneous miscarriage, and increased risk of obstetric complications.

Objective

Our objective is to analyze the reasons behind this increasing tendency for women to have children later in life, to study the clinico-biological characteristics of these patients, and the results of our center.

Methods - Patient(s)

We have conduct a retrospective study in our center in Tunisia. The women whose age at the time of study was 38 years or older were included. The duration of the study spanned 7 years. Any procedure of ARTs that was done before the age of 38 was excluded but taken into consideration.

Results

In our study, beyond the age of forty, the rates of pregnancy and childbirth declined markedly and were 43% and 6.25%, respectively. other hand, the rate of miscarriage increased (28.12% in our study). From the age of 40, most teams advocate for IVF at the outset. The ultrasound measurement of the antral follicular count makes it possible to assess the prognosis in terms of pregnancy and delivery rates.

Conclusion:

The longer duratin of higher education and the delay in obtaining a stable work situation partly explain a later desire for pregnancy among these couples. Nearly 12% of the patients consulted for secondary infertility within the current marriage and previous pregnancies had occurred outside the ARTs in 60%

MAP and fertility preservation

Follicle populations and vascularization in human pediatric ovarian tissue after long-term grafting

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Context

Data on ovarian tissue from prepubertal patients are scarce, with very few studies conducted so far. What is known is that the proportion of quiescent follicles remains elevated after grafting and only a small percentage initiate growth.

Objective

The aim of the study was to evaluate the difference between pediatric and adult ovarian tissue in terms of follicle populations and development, and ovarian vascularization, before and after long-term xenografting.

Methods

Ovarian tissue biopsies were each divided into three pieces: one was processed for histology, another for transmission electron microscopy (TEM), and the third was grafted to immunodeficient mice for 20 weeks.

Patient(s)

Ovarian tissue from 5 young girls (mean age: 3 years) and 7 adult women (mean age: 27.8 years) was investigated.

Intervention(s)

We performed hematoxylin and eosin staining and immunofluorescence analysis for human von Willebrand factor, murine CD31, and aSMA.

Main outcome measure(s)

In both groups, follicle density, ultrastructure, morphology, classification and size were evaluated before and after grafting, as well as vessel density and endothelial area.

Results

Follicle density was higher in pediatric patients than adults (p=0.01) and fell significantly with age and after grafting. Quiescent-stage follicles made up most of the follicle pool in young girls (71.5%), while growing follicles were scarce (1%). Follicles with abnormal and atretic morphological features were also observed in pediatric tissue (9.5% and 18.2% respectively) and both declined with age and grafting. Quiescent follicle numbers remained high after grafting (64.3% in girls and 66.8% in adults), while growing follicle rates stood at 27% in both groups. Vascularization analysis revealed more and larger immature vessels in pediatric tissue (p=0.007, p=0.009) before grafting, but no difference with adult tissue after grafting. Indeed, more and larger mature vessels were found after grafting in the pediatric group. TEM of pediatric follicles showed a different arrangement of cytoplasmic organelles and abnormal follicles characterized by loss of shape and vacuolization of cytoplasmic content, without organelle damage.

Conclusions

Ovarian tissue from very young patients behaves differently from ovarian tissue of older prepubertal and adult subjects, as it appears to respond to external stimuli in a more uncontrolled way, as well as being differently vascularized.

MAP and fertility preservation

Melatonin effect on cryopreserved ovarian tissue

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Context
Recent improvements on the treatment of cancer have provided prepubertal patients longer survival. This scenario has demanded new techniques to preserve ovarian tissue to enable fertility preservation and reproduction after treatment

Objective
To analyse the influence of melatonin aplication on the cryopreservation medium on ovarian tissue structure and function

Methods
Rats were submitted to intact whole ovary freezing for 24h. After thawing, grafts were analysed
Animals. Six adult female Wistar rats presenting regular estrous cycle

Interventions
The animals were distributed into two study groups (n=3 each): 1) Control (CT); 2) Melatonin (MT) according to the application of melatonin 10-7M diluted to 15µl of cryopreservation medium (MT) or not (CT).

Main outcome measures
Histology (immature and mature follicles, corpora lutea and blood vessels); immunohistochemistry (TUNEL and caspase)

Results
All histological and immunohistochemical analysis showed no statistically significant ($p<0,05$) difference between groups Melatonin and Control: immature follicles (CT 10.33 ± 2,90 Mt 4.66 ± 0.88 p=0.13); mature follicles (CT 11.00 ± 3.51 MT 5.33 ± 1.20 p=0.20); corpora lutea (CT 10.00 ± 3.46 MT 10.33 ± 4.70 p=0.95); blood vessels (CT 4.66 ± 1.45 MT 2.66 ± 1.76 p=0.43); caspase (stroma CT 1.61 ± 0.32 MT 1.95 ± 0.33 p=0.48; follicles CT 3.39 ± 0.75 MT 2.37 ± 0.33 p=0.18); TUNEL (stroma CT 0.05 ± 0.01 MT 0.21 ± 0.09 p=0,05; follicles CT 0.04 ± 0.01 MT 0.07 ± 0.01 p=0.26)

Conclusions
Melatonin effects on ovarian tissue cryopreservation may only be detected after transplantation and not just after thawing

MAP and fertility preservation

Long-term effect of oocyte survived from primordial follicle with cyclophosphamide exposure

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Context
Cyclophosphamide (CTX) is widely used in chemotherapy as an important alkylating agents. It can directly cause primordial follicles loss and induce ovarian function damage. However, a small percentage of primordial follicles can still survive from CTX toxic insult and continue to develop. These oocytes' fate is not clearly established.

Objective
To determine whether cyclophosphamide would have long-term detrimental effect on survived oocytes and evaluate the folliculogenesis of patients had chemotherapy before.

Methods
After follicles developed to antral stage post-injection. Overall situation was evaluated and both GV and MII stage oocytes were retrieved for function and quality detection. GV stage oocytes were also collected for single-cell RNA-sequencing. Ovary cortexes were used for H&E staining and further analysis.

Patients
Human ovary cortex tissues were collected from patients with malignant tumor aged 18 to 40 years.

Intervention
A single dose of cyclophosphamide or saline was injected to three-week old mice. Patients before gonadotoxicity therapy and others had undergone cyclophosphamide treatment before were divided as two groups.

Main outcome measure
Alteration of body and ovary weight was used to detect the overall toxicity. For oocyte quality, levels of mitochondrial membrane potential, ROS, ATP were measured and distribution of mitochondrial and spindles was stained. IVF was utilized for oocyte function evaluation. For sections, the number and morphology of follicles were counted.

Result
Ovary weight decreased seriously and fewer oocytes were retrieved in CTX group, and MII oocytes exhibited more ratio of abnormal morphology. Both GV and MII oocytes on CTX group showed that reduced JC-1 potential, ATP level and stronger oxidative stress. Moreover, oocytes after CTX injection showed more abnormal distribution of mitochondrial and aberrant spindle morphology. As *in vitro* fertilization, the chemo-group oocytes had lower development fraction. YAP1 was significantly downregulated in CTX GV oocytes versus control. And cortex from chemo patients had less follicles and more abnormal morphology.

Conclusions
This study demonstrated the first time that oocytes exhibited poor quality survived from primordial follicles with CTX exposure, and YAP1 may have important role during this progress. CTX might have long-term adverse effects on oocyte maturation and developmental competency both in mice and human.

Insulin resistance, metabolic syndrome, obesity and PCOS

Insulin resistance in Congolese women with polycystic ovary syndrome: implications of diet

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Context
It is believed that there is a possible association between dietary intake and insulin resistance (IR) in women with PCOS. However, there are limited data that focuses on diet management in Sub-Saharan African women with PCOS.

Objectives
To assess the Congolese dietary intake and its effects on insulin resistance in Congolese women affected by PCOS.

Methods
This prospective case-control study was performed from February 2017 to June 2017, in Kinshasa.

Patients
Fifty-two PCOS women and fifty-two age-matched controls were involved in the study.

Main outcome measures
Fasting biochemical parameters, Homeostasis Model assessment of insulin resistance and body composition using Bioelectrical Impedance Analysis (BIA) were evaluated. Wrist Circumference, Waist Circumference, Hip Circumference, Height and Weight were measured.
Qualitative assessment of dietary intake was performed using a Frequency Food Questionnaire (FFQ), while the quantitative evaluation, was performed using a food diary.

Results
40,4% of PCOS women were insulin resistant ($p < 0,0001$). PCOS women with IR were more obese, with high amount of body and visceral fat ($p<0,05$).
When PCOS with IR were compared with those without IR, there were not significant differences in the mean intake of starches, meat, sweet foods, alcoholic, non-alcoholic beverages, vegetables and fruits consumption. However, mean intake of white rice were significantly higher in PCOS women with IR. Moreover, worsened IR (HOMA-IR > 3,5 mol x $\mu U/L^2$) in PCOS women has been found correlated with daily consumption of white rice. Indeed, 80 % of women with daily consumption of white rice had worsened insulin resistance ($p = 0,015$).
Correlation analysis showed that white rice consumption was significantly correlated with insulin ($r = 0,262$; $p = 0,007$), and HOMA-IR ($r = 0,281$; $p = 0,004$). Negative correlation was observed between insulinemia ($r = -0,072$; $p = 0,469$), HOMA-IR ($r = -0,066$; $p = 0,507$), white rice ($r = -0,174$, $p = 0,078$) and fish consumption.
Logistic regression showed that white rice consumption was the main determinant of insulin resistance in women with PCOS ($p<0,05$).

Conclusion
Several studies have reported on the influence of diet on insulin resistance. Our study provides insight into the effect of white rice on insulin resistance in women with PCOS.
The present findings suggest that a substantial consumption of white rice may induce insulin resistance in PCOS women.

Insulin resistance, metabolic syndrome, obesity and PCOS

Wrist circumference: a new marker of insulin resistance in women with polycystic ovary syndrome

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Context
Insulin resistance, the metabolic basis for developing future cardiovascular disease, is the main complication found in 35-80% of women with Polycystic ovary syndrome (PCOS). However, there is no definite consensus regarding which marker to use for its assessment in PCOS women.

Objectives
The aim of the current study was to assess Wrist Circumference as an easy-to detect marker of insulin resistance in Congolese women with PCOS.

Methods
This study was a prospective case-control study performed from October 2015 to December 2016 in Kinshasa, the Capital City of the Democratic Republic of Congo.

Patients
Seventy-two PCOS women and seventy-one controls were enrolled in the study (mean age 24,33 ± 5,36).

Main outcome measures
Fasting biochemical parameters, Homeostasis Model assessment of insulin resistance and body composition using Bioelectrical Impedance Analysis (BIA) were evaluated. Non Dominant Wrist Circumference were measured manually, as well as Waist Circumference, Hip Circumference, Height and Weight.

Results
Non Dominant Wrist Circumference was the most correlated to HOMA-IR (r = 0,346; p=0,003) than Dominant Wrist Circumference (r = 0,315; p = 0,007), Waist Circumference (r = 0,259; p = 0,028), BMI (r = 0,285; p = 0,016), WHR (r = 0,216; p = 0,068) and WHtR (r = 0,263; p = 0,027). Logistic regression showed that Non Dominant Wrist Circumference was the best anthropometrical marker correlated to insulin resistance using HOMA-IR as biological reference marker in PCOS women (p = 0,016). The diagnostic accuracy of Non Dominant Wrist Circumference for the presence or absence of IR, using ROC curve analysis showed that the area under the ROC curve were 0.72. A cutoff value of Non Dominant Wrist Circumference of 16,3 cm, was found as the best predictor of IR in Congolese women with PCOS.

Conclusion
Non Dominant Wrist Circumference is, to date, the best anthropometrical marker of insulin resistance, in Sub-Saharan African women with PCOS. It could be suggested as an easy-to detect marker for assessing IR in women with PCOS. Our findings open new perspectives in the correlation between insulin resistance and bone homeostasis in PCOS women.

Insulin resistance, metabolic syndrome, obesity and PCOS

Hypoalbuminemia in female obesity. An observational study in obese patients undergoing bariatric surgery

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Context
In current literature the interaction of hypoalbuminemia and BMI was independently associated with complications in different surgical fields. Hypoalbuminemia is an independent risk factor in obesity and in bariatric patients, but also an important biomarkers of protein malnutrition.

Objective
Our purpose of is detect the association between Hypoalbuminemia and protein malnutrition in a population of obese patients undergoing bariatric surgery, a 30 days outcome, and what disorders are associated. We defined Hypoalbuminemia as a serum level < 3,4 mg/dl

Methods
We performed a prospective observational study use the Bariatric Surgery benefit/risk calculator from metabolic and bariatric surgery accreditation and Quality imperilment Program. The values we collected and modified were Any compliance, severe compliance, Readmission. Was performed also the Charlson Comorbidity Index.

Patients
26 obese patients requiring bariatric surgery recovered in Candela Casa di Cura from May to July 2019. The preoperative assessment of laboratory medicine, cardiology, pneumology and radiology was the first step. Age 41,6 + 1,19., we selected a cohort of patients with albumin levels under 3,6 mg/L (59 %), BMI score, biochemical assessment related to nutritional problems.

Main outcome measure
Unfavourable outcomes at 30 days after surgery (Any o Severe complications, Readmission)

Results
The percentage of 84% of morbid obesity (BMI > 40) was detected, The bariatric Surgery risk/benefit was respectively in group "Any compliance " range 4,90-2,41(3,0),"Severe Compliance "2,34-1,69 and in the Readmission group 2,93-1,61. The Charlson Comorbidity index range was 3,4 %- 20,4 % with high prevalence of Metabolic Syndrome (27 %) and Osas (22 %).

Conclusion
Hypoalbuminemia perform a low-grade inflammation, and an excess of fatty acid as cause of metabolic dysfunction in skeletal muscle a disorders of morbid obesity. Serum albumin is a negative acute phase reactant, so decrease as consequence of hepatic positive acute -phase reactant. This metabolic condition, more than a predictor of complications, is a altered redox biochemical state in female Obesity.

Insulin resistance, metabolic syndrome, obesity and PCOS

Ovarian stimulation and clinical outcomes following *in vitro* fertilization procedures: is there effect of overweight and obesity?

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Context

Overweight and obesity are known risk factors for fertility; however there is poor consistent data about its effect on *in vitro* fertilization (IVF).

Objective

Analyze the impact of Body Mass Index (BMI) on controlled ovarian stimulation response and pregnancy rates, in patients who underwent IVF.

Methods

Retrospective case-control study, 2013-2018, performed at Fertilitat - Reproductive Medical Center, Brazil. Sample was divided into two analysis: ovarian stimulation response and pregnancy rates. Sample size calculated was 109/group.
Patients: Total of 298 patients were included: 546 follicular aspiration cycles for IVF divided into three groups for first analysis, according to BMI(kg/m^2): G1)BMI<25(n=236);G2)25-29.9(n=235);G3)≥30(n=75); and 636 embryo transfers cycles, also divided into groups according to BMI for second analysis: G1)BMI<25(n=347);G2)25-29.9(n=233); G3)≥30(n=56).

Main outcome measures

Data presented as median(IIQ) or n(%). ANOVA and Chi-square tests were applied, considering p<0.05.

Results

First analysis: comparing G1 vs. G2 vs. G3, following results were found, respectively: aspirated oocytes (10.5 [6-15.7] vs. 7.5 [4-12] vs. 6 [2-12]), p <0.001; mature oocytes (8 [5-12] vs. 5 [3-9] vs. 4 [2-8]), p <0.001; oocyte maturity index (83% vs. 78% vs. 69%, p <0.03). When compared only G1 vs. G2, the significant difference on oocyte maturity index was missed (p=0.102). However, when comparing G2 vs. G3, this difference was observed (p=0.029). For G1 vs. G3, all variables were p<0.001. Comparing G1+G2 vs. G3, results found were, respectively: median aspirated oocytes (9 [5-15] vs. 6[2-12], p=0,001), median mature oocytes (7 [3-11] vs. 4 [2-8], p<0,001) and oocyte maturity index (0,8 [0,7-0,9] vs. 0,69 [0,5-0,8], p=0,002). Second analysis: there was no significance between biochemical/cycle (40% vs. 36.4% vs. 35.7%, p=0.626), clinical/cycle (30,2% vs. 29,6% vs. 23,2%, p=0,56) or cumulative pregnancy rates (76.3% vs. 68.6% vs. 71.4%, p=0.112), not even when those variables were compared only between G1 vs. G3 (p<0,05).

Conclusion

Patients with normal BMI showed better ovarian stimulation response than other groups, while obese women had the lowest oocyte maturity index. Despite ovarian stimulation results, there was no translation into clinical outcomes. In this study, overweight and obesity does not appear to have a direct effect on IVF outcomes, but seems to have a negative effect on ovarian stimulation.

Insulin resistance, metabolic syndrome, obesity and PCOS

Obesity in puberty. Reproductive effects

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An assessment of the puberty obesity's effect on the reproductive function has not been studied.
The aim of the study is to assess the reproductive function in women with metabolic disorders in the puberty and to identify markers of reproductive disorders.

Design

A prospective study of 170 teenage girls with metabolic disorders was conducted between 2000 and 2013. At the reproductive age, 86 women were included in the study and 84 women were excluded (13 were with tubal infertility, 26 were below reproductive age, 23 used contraception, 22 changed their place of residence). The body mass index in the puberty was 31.1 ± 0.35 kg/m^2, in the reproductive age - 24.7 ± 3.9 kg/m^2.

Method

General clinical, gynecological, laboratory and instrumental methods of research. Determination of hormone concentrations was performed by competitive solid-phase enzyme immunoassay using test systems "Alkor-Bio" (Russia) on the enzyme immunoassay Cobos ELL (USA).

Results

As part of a prospective study, it was found that 53.5% (95% CI: 43.03–63.66) were fertile, 30.2% were primary infertile (95% CI: 21.54–40.61), and 16.3% were secondarily infertile (95% CI: 9.95–25.49). Significant prognostic markers of the reproductive age's primary infertility in women with metabolic disorders in past medical history, obtained by constructing a model (χ2=37.8, p=0.001) are a decrease of the anti-inflammatory cytokine (IL-10) in the blood serum (OR= 0,57; 95% CI: 0.35–0.93), glycodeline in menstrual blood (OR = 0.78; 95% CI: 0.61–0.99) and increased LDL cholesterol (OR = 11.21; 95 % CI: 1.43–87.59).

Conclusions

Thus, a prospective study showed that 30.2% of reproductive age women with metabolic disorders in the puberty have primary infertility, which is caused by a low-intensity inflammatory process, a violation of the protein-forming function of the endometrium and lipid metabolism.

Insulin resistance, metabolic syndrome, obesity and PCOS

Bone mass in women with polycystic ovary syndrome: an yin-yang tale?

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Context
Polycystic Ovarian Syndrome (PCOS) is a highly prevalent gynecological disorder with a complex pathophysiology. It affects 5-15% of reproductive-aged women. This condition is characterized by clinical and/or biochemical hyperandrogenism and chronic anovulation. Hyperinsulinemia is also a common finding, affecting 50-75% of PCOS women. Androgens are thought to improve bone mass and insulin seems to be detrimental.

Objective
This study aims to assess bone density in women with PCOS, compared with age-matched controls.

Methods
This was a cross-sectional study including 51 PCOS women and 21 age-matched controls. PCOS was defined by Rotterdam criteria after the exclusion of other causes of hyperandrogenism and menstrual irregularity. All women were in the current use of cyclic oral contraceptive pill. Bone density was assessed by Dual-energy X-ray absorptiometry (DXA). Women were recommended to collect blood samples for hormonal measurements on the third day of menstrual cycles.

Results
Mean age was 29.4 ±5.6 vs 30.7 ±7.5 years old (PCOS vs control group, respectively, p=0.43). Body mass index (BMI) [35.1± 6.5 vs 29.3 ± 6.1 kg/m^2, p=0.001] and as expected total testosterone levels [57 ± 26 vs 27 ± 9 ng/dL, p=0.0001] were higher in the PCOS group compared to controls. HOMA-IR was similar between PCOS and control groups [8.61 ± 10.39 vs 4.30 ± 1.40, p=0.33]. Vitamin D levels did not differ between groups [19.7 ± 6.3 vs 21.6 ± 6.5, p=0.39]. Regarding bone parameters, lumbar BMD was increased in the PCOS group [1.29 ± 0.14 vs 1.19 ± 0.15 g/cm ^{3}, p=0.02], as well as femoral neck BMD [1.10 ± 0.16 vs 0.96 ± 0.12 g/cm ^{3}, p=0.004] and total femoral BMD [1.34 ± 0.15 vs 1.00 ± 0.11 g/cm ^{3}, p=0.002]. However, after controlling for BMI, only total femoral BMD persisted increased in the PCOS group (p=0.03). There was a trend towards an increase in femoral neck BMD in the PCOS group (p=0.052), whereas lumbar spine BMD was not different (p=0.12).

Conclusion
Our preliminary data show that PCOS women had an increase in femoral bone density, which seemed to be independent of BMI. We hypothesize that androgens primarily promote periosteal bone acquisition in cortical bone, which is mainly evaluated by femoral measurements, and could be one factor involved in this finding. Studies with larger sample size and bone microarchitecture evaluation could better elucidate this finding.

Insulin resistance, metabolic syndrome, obesity and PCOS

The impact of polycystic ovary syndrome phenotypes on the risk of developing metabolic syndrome-associate diabetes: a six-year follow-up

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Metabolic syndrome (MS) in women with polycystic ovary syndrome (PCOS) has been assumed to be a progressive disorder; however, confirmatory follow-up data supporting this hypothesis, and whether the specific PCOS phenotype impact progression are lacking. The aim of this study was to evaluate the influence of PCOS phenotypes (Phenotypes A-D) and treatment modality on the morbidity of MS, and the development of T2DM, in PCOS. In this retrospective observational study, we initially identified 441 PCOS patients diagnosed by the 2003 Rotterdam criteria that had been followed longitudinally. All subjects underwent a baseline 75 g oral glucose tolerance test measuring both glucose and insulin, and underwent measurement of total testosterone, and lipid profile. The diagnosis of MS was made if subjects met three of the five NCEP-ATP III criteria. Type 2 diabetes mellitus (T2DM) was diagnosed by the ADA criteria. Therapies administered included metformin (MET) prescribed for patients with insulin resistance (IR)/hyperinsulinemia (HI), impaired glucose tolerance (IGT), obesity or T2DM. Patients with neither MS nor reproductive desire were prescribed a hormonal contraceptive (HC) with ethylestradiol 35 μg and cyproterone 2 mg for menstrual irregularity, along with spironolactone (100mg/day) for hirsutism, if present. PCOS phenotypes were defined as follows: A - clinical or biochemical hyperandrogenism (HA) + ovulatory dysfunction (OD) + polycystic ovary morphology (PCOM); B - HA + OD; C - HA + PCOM; and D - OD + PCOM. The data were analyzed using Student's t and Pearson's chi-square tests. Multivariable analysis was applied to evaluate the effect of the PCOS phenotypes on the risk for MS and T2DM. PCOS patients with Phenotype A demonstrated the highest risk for T2DM (OR=0.406 [1.395 to 11.85]) compared to other phenotypes. Patients were subdivided into two groups: those with (MS; n=68) and those without (No-MS; n=192) MS. Of PCOS patients with MS 60% (41/68) were using MET (n=41), while patients without MS preferably used hormonal contraceptives (n=117). The main indication for MET use in the MS group was IGT (n=23). Among PCOS women with MS the most prevalent PCOS phenotype was type A (n=32). In No-MS PCOS patients, the most common indications for MET use were IR/HI (n=18). Over the period of follow-up the severity of metabolic abnormalities tended to decrease with MET administration and to increase with the use of HC. Phenotype A was associated with the highest risk of developing T2DM during the follow-up period. The use of MET, at least when administered for IR/HI or IGT, did not seem to decrease the risk of developing T2DM in our cohort.

Insulin resistance, metabolic syndrome, obesity and PCOS

Binge eating disorder (BED) – an independent risk factor of anxiety and depressive symptoms in women with polycystic ovary syndrome (PCOS)

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Context

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women of reproductive age, with a prevalence of up to 15%. Its diagnosis is made by using Rotterdam criteria. The occurrence of PCOS is associated with an increased prevalence of depression and anxiety symptoms and with metabolic disturbances such as obesity. Obesity, insulin resistance, and elevated androgens may partly contribute to this association. The results of a meta-analysis indicate that the mean prevalence of obesity among women with PCOS is 49% A review of the literature indicates a higher prevalence of binge eating disorder (BED) in this group than in the general population, which varies from 12% to 39%. Diagnosis of BED is important because it can successfully be treated with behavioral intervention, psychoeducational intervention, psychotherapy.

Objective

To asses the prevalence of BED in polish PCOS women and its' impact on depression and anxiety symptoms among that group of women.

Method

Diagnosis of PCOS was made using Rotterdam criteria. Binge Eating Disorder was diagnosed according to DSM-5 criteria. Depressive and anxiety symptoms were measured by the Hospital Anxiety and Depression Scale (HADS). Statistical analysis was conducted using IBM SPSS Statistics (v.25) software.

Patients

A total of 128 women with PCOS aged between 16 and 45 and hospitalized at the Gynecological Endocrinology Department of the Medical University of Warsaw between June 2017 and September 2018.

Results

Among PCOS women 65,9% presented anxiety symptoms and 30,5% depressive symptoms. 42% of all women with PCOS met DSM-5 criteria for BED. In PCOS women with BED anxiety symptoms are present in 77,4% vs. 58,8% in PCOS women without BED (p=0,017). Depressive symptoms are present in 54,8% of PCOS women with BED vs. 15,7% in PCOS women without BED (p=0,002). The mean value of anxiety symptoms in PCOS women with BED in comparison to PCOS women without BED is 12,55 vs. 8,94 (p=0,002) and the mean value of depressive symptoms is 7,29 vs. 4,12 (p<0,001).

Conclusions

The prevalence of anxiety and depressive symptoms among PCOS women is higher in comparison to non PCOS women. The prevalence of BED in PCOS women is higher than in non PCOS women. Among PCOS women with BED prevalence and the mean aggravation of anxiety and depressive symptoms is higher than in PCOS women without BED. PCOS women with BED are under a higher risk of anxiety and depressive disorders and in this group a routine screening for BED as well as for anxiety and depressive symptoms should be performed.

Insulin resistance, metabolic syndrome, obesity and PCOS

Metabolic syndrome as a risk factor for vascular complications in patients with endometrial cancer

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Context
Endometrial cancer remains one of the most important issues in gynecologic oncology, it requires timely diagnosis as well as prevention of adverse postoperative outcomes. Endometrial cancer is associated with high risk of
developing venous thromboembolic complications, particularly in patients with obesity. Therefore, patients at high risk need rational prevention of thromboembolic complications.

Objective
To determine the activation level of hemostasis system in patients with endometrial cancer for analyzing the effectiveness and safety of treatment with antithrombotic therapy when surgeries are performed.

Patients
The study included 80 patients diagnosed with a verified diagnosis of endometrial cancer, including 56 cases staged T1bNxMx, and 24 cases staged T2aNxMx.

Methods
In order to perform comparative analysis of hemostasis system and to study the effectiveness of antithrombotic therapy, the patients were divided into two groups according to pathogenetic patterns: patients with normal body weight (n = 40) and patients with obesity (n = 40). Forty women were healthy controls.

Interventions
All patients underwent laparoscopic total hysterectomy, adnexal surgery and pelvic lymphodenectomy.

Main outcome measures
The main parameters of hemostasis system in both groups were analyzed, and mutation in genes affecting hemostasis in such patients was revealed.

Results
According to the study, the functional reserves of hemostasis system are more diminished in obese patients with endometrial cancer than in patients with normal body weight, therefore it is necessary to perform effective antithrombotic therapy. Preoperative anticoagulant therapy in combination with postoperative treatment with low molecular weight heparin (parnaparin-natrium) may prevent the development of venous thromboembolic complications even in patients at high risk.

Conclusion
Taking into consideration the unstable hemostasis system in obese patients with endometrial cancer, the use of parnaparin-natrium appeared to be highly effective in the prevention of thrombotic complications after surgery in patients with endometrial cancer.

Insulin resistance, metabolic syndrome, obesity and PCOS

A NK3Ra ameliorates metabolic disorder in mice by improving adipocyte mitochondrial function

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Neurokinin B (NKB) acts as an important modulator of reproductive function by binding with neurokinin-3 receptor (NK3R). NK3R antagonists have emerged as new therapies for some reproductive endocrine conditions, such as perimenopausal hot flashes and PCOS. Metabolic state changes can regulate NKB/NK3R expression, but it is not clear whether NK3R antagonists (NK3Ras) affect metabolism. Therefore, we explored the metabolism-regulating role and mechanism of an NK3Ra in a constructed metabolic disorder mouse model and the 3T3-L1 mouse adipocyte cell line. The results showed that the NK3Ra SB222200 significantly reduced body weight in mice with metabolic dysfunction; significantly reduced adipose tissue levels; significantly improved serum lipid metabolism and an inflammatory factor index; and significantly increased serum adiponectin levels and upregulated UCP1 expression while downregulating Fabp4 and PPARγ expression in white adipose tissue. *In vitro*, NKB treatment significantly increased FABP4 and PPAR γ expression and decreased Nrf1, FIS1 and NNT expression in 3T3-L1 cells, while SB222200 reversed these changes; these results were further confirmed with NK3R-overexpressing 3T3-L1 cells. To determine whether SB222200 affects brown adipose tissue, we detected the expression profile of brown adipose tissue via RNA-seq and found increased expression of several myogenic signature molecules in the NK3Ra group. We conclude that NK3Ras can directly act on both white and brown adipocytes, promote energy consumption by improving mitochondrial function in cells, and play roles in reducing body weight and ameliorating metabolic disorders in mice.

MAP: follicle selection, embryo implantation, immune system and oxidative stress

The impact of artificial intelligence on Farid's updated innovation in reproduction

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Introduction

Every second passed there is a new in reproductive medicine. Artificial intelligence (AI) is partnership between man and machine. So the aim of this work is to represent the updated innovation in the last 3 years of the author under the impact of artificial intelligence.

Material and Methods

Artificial intelligence applied to text mining with network information input for the web based tool. the algorithm features an adjustable threshold to increase either sensitivity or specificity.

The clinical decision support system using algorithm that present a high precision: multi layer perception, Deep Learning, support Vector machine and Naives Bayes we proposed a Novel deep learning method regarding the effect of cerebrolysin, olive oil, Bee venom on poor responder in prospective strong effect of Bee propolis on oocyte aging, the effect of Farid syrup(Honey: Bee Propolis: zamzam water with ration 3:2:1 respectively) on Mitochondrial function and DNA damage. Nano gold in experimental endometriosis and adenomyosis. Magnetic and Bee venom acupoint stimulation treatment of unexplained infertility, a new estrogen receptor delta, treatment of arteriovenous malformation by interferon through trans vaginal ultrasound.

Results

Using artificial intelligence Deep learning, we demonstrated positive impact of cerebrolysin, olive oil, Bee propolis on poor ovarian responders, effect of Bee propolis on aged oocyte, positive impact of Farid syrup on mitochondrial function and DNA damage, the curative effect of Nano gold on endometriosis, Adenomyosis, high pregnancy rate, live birth rate after magnetic and Bee venom acupoint stimulation, Delta new estrogen receptor and high pregnancy rate after interferon treatment of arteriovenous malformation as a cause of foetal wastage.

Conclusion

Using artificial intelligence we demonstrated positive impact of Bee propolis, Farid syrup, olive oil, Bee venom,(poor responders) Bee venom and magnetic acupoint stimulation on unexplained infertility, interferon treatment of repeated fetal wastage, new estrogen receptor Delta and its chromosomal localization.

MAP: follicle selection, embryo implantation, immune system and oxidative stress

Immunohistochemical patterns of vitamin D effects on successful implantation

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Context

The contemporary world despite its enough developed medicine and generally highly en-lightened population faces a great problem of vitamin, micro-element and nutrient deficiency turning to become the XXI century pandemic. Along with that significant growth of interest can be seen towards vitamin D importance for reproductive physiology. Fact is that vitamin D receptors (VDR) have been detected in women's ovarium tissue, fallopian tubes, decidua and placenta. Some latest years studies have proved that vitamin D may act as immune regulator during implantation. The non-classical effects of vitamin D are highly important during pregnancy - it induces decidualization, limits production of proinflammatory cytokines what can help in normalizing process of implantation in early pregnancy.

Objective

The purpose of this study is to compare the expression of vitamin D and its receptor in the villous chorionic villous among the missed abortion and induced abortion groups and level of 25(OH)D in the blood of women.

Methods

It was a prospective complex cohort study which included pathomorphological investigation.

Patients

The pathomorophology included 64 cases of abortion material from women with missed (group 1- n=32) and induced abortion with normal pregnancy (group 2 - n=32).

Interventions

The state of vitamin D was based on the concentration of 25(OH)D, determined by enzyme immunoassay in the mother's serum. Pathomorophological investigation included haematoxylin and eosin stain (H&E stain), immunohistochemistry (IHC) and confocal laser scanning microscopy (CLSM) with 3D reconstruction of vitamin D and VDR expression in abortion material (chorionic villus).

Main outcome measures and results

The immunohistochemical study showed homogenous distribution of vitamin D and VDR expression in syncytiotrophoblasts, cytotrophoblasts and chorion villus stroma both in missed abortion group and comparison group. Vitamin D and VDR expression relative area in missed abortion group statistically significant lower than in group 2 ($p<0,01$). There was found significantly positive correlation between vitamin D blood-level and VDR expression relative area ($r=0,41$) in group 2.

Conclusion

Based on our study, we can conclude that Vitamin D protectively influence on pregnancy prolongation and development during 1 trimester. Vitamin D deficiency may be associated with pregnancy complications such as spontaneous abortions.

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Autoimmune screening: our experience in an infertile sample of women

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Context
The association between autoimmune diseases and reproductive problems is well established, however little is known about the significance of subthreshold autoimmunity in a healthy population seeking treatment for infertility.

Objective
To determine if a nonspecific autoimmune screening has a clinical significance in a sample of women evaluated in an infertility centre at first consultation.

Methods
Retrospective observational cross-sectional study over 18 months at the Center of Reproductive Medicine, IRCCS Policlinico San Matteo, University of Pavia. Infertile women (n=241) without any previous diagnosis for autoimmune/rheumatic disorders underwent both to a screening questionnaire for signs and symptoms and to antinuclear antibodies (ANA) testing (IIFT, 1:80). Clinical features and markers of ovarian reserve were considered for appropriate statistical analysis.

Main outcome measures
The median age was 37 years, with 25.7% overweight/obese and 23.3% smokers. In 38.6% of cases female infertility was diagnosed, whereas male infertility was present in 12.4%, mixed in 30.5% and unexplained in 18.5%. ANA positivity affected 45.8% of our sample and positive women were significantly older (37.5 vs 36.0 yrs, p=.04). Antimullerian hormone (AMH) was lower in the ANA-positive group (median 1.59 ng/ml vs 2.4 ng/ml, p=.004) and 70% of women with low antral follicular count (AFC) (<5 follicles) had ANA positivity (vs 42.8% in AFC 5-15 group and 41.8% in the >15 group (p=.002). Only in women >35 years, ANA positivity was associated with low (<1.2 ng/ml) AMH values (54.7% vs 29.7%, p=.002) and low AFC (26.7% vs 9.5%, p=.01). At least one positive answer to the screening questionnaire was given by 160 women (66%), without any significant difference between positive and negative ANA screening. Indeed, only a trend of a positive screening was found in ANA-positive (48.1%; n=77/160) as compared with ANA-negative (37%; n=30/81). The most frequent symptoms were recurrent miscarriage, photosensitivity and Raynaud phenomenon, irrespectively of ANA detection.

Results
Even a mild ANA positivity was associated to a lower ovarian reserve in older infertile women. A self-administered questionnaire did not seem useful to identify ANA-positive patients in this specific population.

Conclusions
Autoimmune screening could be useful in infertile women over 35 years to identify those with possibly poor assisted reproductive technology outcomes but further studies are warranted.

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Vaginal *Lactobacilli spp.* and inflammatory biomarkers in pre-menopausal and post-menopausal women

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Context
The characterization of vaginal Lactobacilli spp. and inflammatory biomarkers could be complex. The presence of lactobacilli within the vagina has been associated with maintaining a healthy vaginal microbiome. Age, menstruation, and estrogen levels can affect the vaginal milieu. The onset of post-menopause is related to low systemic inflammatory status, manifested by increased levels of several cytokines. The difference between lactobacilli profiles and cytokine expression between pre-menopausal and post-menopausal women is not fully understood.

Objective
The study objective is to evaluate the differences in the vaginal microbiome and inflammatory biomarkers of pre-menopausal and post-menopausal asymptomatic women.

Methods
A retrospective database review was performed using patient info from IRB Protocol Database #13006 ASR. Patient data was analyzed with specific attention to lactobacilli presence, and cytokine quantification. Lactobacillus spp. were analyzed using quantitative PCR (qPCR) that identified L. jensenii, L. crispatus, L. iners and L. gasseri. Cytokine analysis of vaginal swab samples was performed using Bio-Plex® 200 systems (Bio-Rad, USA) and Quick Plex SQ 120 (Meso Scale Discovery, USA). A total of 27 cytokines were analyzed using the multiplex assay kit. Data was analyzed using GraphPad Prism and R. The samples were tested using the median test.

Patients
Study groups consisted of asymptomatic, non-pregnant, healthy women, aged 21-75 years with no previous history of chronic or recurring vulvovaginal conditions. Sample populations consisted of 15 pre-menopausal and 15 post-menopausal patients.

Results
Microbiome analysis showed colonization of L. iners in 60% of the pre-menopausal population, and 20% of the post-menopausal population.
Of the 27 cytokines tested, 6 were determined to have a statistically significant difference between pre-menopausal and post-menopausal groups. TNFα, G-CSF, IL-6, and IL-8 were expressed at elevated levels in the post-menopausal group. The pre-menopausal group showed elevated levels of IL-12-p70 and GM-CSF compared to their post-menopausal counterparts. ($p < 0.05$)

Conclusions
Lactobacilli colonization by L. iners was noticeably higher in pre-menopausal women.
An increase in the pro-inflammatory cytokines TNFα, Il-6, and Il-8 was observed in the post-menopausal group which points to a dysregulation of the immune system often observed in post-menopausal women.

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Fresh versus frozen-thawed embryo transfers and the perinatal outcomes

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Context
Studies have evaluated whether there is any relationship between pregnancies from frozen embryos (FET) with fetal weight and percentile at birth. However, existing data is still insufficient to determine any type of correlation in this sense.

Objective
This study intends to evaluate neonatal outcomes, regarding birth percentile, gestational age and birth weight stratifications, after FET transfer compared to fresh embryo transfer cycles.

Methods
Retrospective case-control study performed at an assisted reproduction clinic in Brazil. Data refers to a period from 2010 to 2019 and were collected from electronic records. Samples were divided into two groups: Group 1 - fresh embryo transfer (n=1443) and Group 2 - FET transfer (n=486)

Patients
A total of 1929 embryos were analyzed

Main outcome measures
Categorical variables were expressed as percentage and were compared with Chi-square test, considering $p<0.05$.

Results
The main findings when comparing group 1 versus group 2 were: percentile<10 (15.2% vs. 7.4%); gestational age < 34 weeks (7.8% vs. 3.1%); birth weight ≥2500g (76.9% and 92.2%), $p<0.001$.

Conclusion
In the present study births from singleton pregnancies following FET was associated with high birth weight and decreased incidence of preterm birth and small for gestational age rates when compared to fresh transfer cycles. Multiple biological mechanisms have been proposed to explain better results of frozen transfers on neonatal outcomes. It could be explained by the following process: controlled ovarian hyperstimulation results in a supraphysiological oestradiol environment, an altered endometrial perfusion, receptiveness and placental dysfunction, which affect embryo implantation and fetal growth. Also, freezing and thawing may promote embryo selection allowing only stronger embryos to survive. However, is being reported that frozen embryo may result in the large baby syndrome which could be explained by epigenetics changes that could occur during early embryo changes caused by freezing and thawing process. Our data corroborates with literature. Nevertheless, more studies are important to elucidate this findings, which would be very important for the future of IVF programmes.

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Insulin-like Growth Factor-I in human oocyte *in vitro* maturation

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Context
Oocytes at the MI or GV stages could potentially increase the total number of available oocytes for fertilization. Cumulus cells (CC) surround oocytes and have a great value for their maturation. Loss of communication between CC and oocytes after denudation in IVF treatment cycle prior ICSI decreases their capacity for maturation. Numerous growth factors mediate CC and oocytes interactions. Among them there is insulin-like growth factor-1 (IGF-1) which promotes cumulus expansion, as well as expression of extracellular matrix involved in cumulus expansion, and increase an estrogen and progesterone production in CC.

Objective
The purpose of the study was to evaluate the maturation capacity and fertilization outcomes of *in vitro* matured human oocytes in medium supplemented with insulin growth factor-1 in the presence of cumulus cells.

Methods
Oocytes were picked up after controlled ovarian stimulation After denudation the oocytes maturity were evaluated and GV stage oocytes were underwent IVM in presence or absence of IGF-I and cumulus cells.

Patient(s)
Immature oocytes from 29 ART cycles were *in vitro* matured and further fertilized with the written consent of patients who underwent treatment in Medical center "ART-clinic of reproductive medicine" from April 2018 to April 2019.

Intervention(s)
All GV stage oocytes (n=96) were divided into three groups: matured in fertilization medium (group 1), matured with the presence of cumulus cell (group 2), cumulus cell and IGF-1 (group 3). The maturation rate was assessed by extrusion of the first polar body, fertilization rate and embryo development were estimated up to 5-th day.

Main outcome measure(s)
In vitro maturation of GV stage oocytes with the presence of cumulus cells and oocytes could be proposed as effective method for human oocytes maturation.

Result(s)
Maturation rates of oocytes were 40.3, 60.2 and 87.2% in groups 1-3, respectively. Only 23.5% of matured oocytes were fertilized in group 1 and 52.5% and 82.5% in groups 2 and 3. 58% of embryos continued their development up to blastocyst stage in group of oocytes matured with the presence of IGF-I and cumulus cells. There was no blastocyst in other groups.

Conclusions
Our findings have shown that IGF-I can improve the oocyte's maturation, fertilization rates of *in vitro* matured GV stage oocytes. Only in the case of the presence of IGF-I and cumulus cells the matured oocytes after subsequent fertilization were able to form blastocysts.

MAP: follicle selection, embryo implantation, immune system and oxidative stress

Application of platelet-rich plasma in assisted reproductive techniques: ovarian rejuvenation therapy

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Context

There is the wide field of PRP application, in particular in reproductive medicine. PRP therapy is investigated in women with premature ovarian failure (POF), infertile women more than 35 years of age, and women with low ovarian reserve. Treatment with PRP is referred to as ovarian rejuvenation.

Objective

To examine the influence of the PRP-injection into the ovary to get the oocytes in patients over 38 years old in *in vitro* fertilization (IVF) cycle.

Methods

PRP was injected into the ovary under ultrasound guidance in perimenopausal women with poor ovarian reserve. Serum levels of follicle-stimulating hormone (FSH) and estradiol (E2) were measured by radioimmunoassay. The ovarian rejuvenation was checked 1-3 months after PRP-treatment. T-test was used for data analysis.

Patients

PRP therapy was performed for 32 perimenopausal women with the middle age 41.09±3.93 years old. All cases underwent unsuccessful natural IVF cycles in the past (no oocyte was obtained).

Interventions

PRP was injected into the ovary under ultrasound guidance on the 9-11 day of the menstrual cycle. The level of the hormones FSH and E2 was measured in patients on the 3rd day of the menstrual cycle with PRP-injection and in the next menstrual cycle after PRP-procedure. The fact of ovarian rejuvenation was confirmed by ultrasound test.

Main outcome measures

The average number of the antral follicles in patient before the PRP-injection was 2.4±1.3. The average level of FSH and E2 in the mentioned group of patients before the PRP therapy was 62.23±44.98 pg/mL and 22.74±16.26 IU/L respectively. After the PRP ovary injection the average level of FSH and E2 was 71.29±42.06 pg/mL and 19.77±17.88 IU/L respectively.

Results

The ovarian rejuvenation after PRP injection was observed in 16 women in 3 months after procedure. The number of the antral follicles on the 5th day of the menstrual cycle was significantly higher after PRP application: 6.3±1.4 vs. 2.4±1.3 respectively ($t = 2.04$, $df=62$, $t_{critical}=1.99$, $P=0.046$). There was no significant difference in FSH and E2 levels after PRP ovary injection. The IVF cycles were performed for 12 women from examined group. The mature MII oocytes were obtained for 7 of them.

Conclusion

PRP is an innovative therapeutic modality effective for the ovarian rejuvenation. Treatment with PRP could be considered as method to get oocytes in perimenopausal women.

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The sensitization value of women to partner sperm in inflammatory genesis infertility

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Objective
Sensitization in women to partner sperm is a known factor in the development of infertility. Allergic reactions to sperm antigens can be manifested by both local and general allergic reactions. All this must be considering in the treatment of infertility, as well as in IVF procedures. The purpose of the study was determination of antisperm serum IgE antibodies in infertile women suffering from pelvic inflammatory diseases.

Materials and methods
We examined 40 women of reproductive age suffering from infertility of inflammatory etiology. The average age was 29 ± 0.6 years. The control group consisted of 16 healthy women of the same age. To determine antisperm serum IgE, we used a modified Anti-Spermatozoa Antibody protocol - ASA Serum ELISA, Demeditec Diagnostics (Germany). The modification is designed to detect only antisperm IgE antibodies that carry Fab fragments to sperm antigens.

Results
The survey showed that in 25 (62.5%) patients, along with various types of opportunistic vaginal microflora, chlamydia, cytomegalovirus, herpes simplex virus, ureaplasma, and their associations were found. Specific IgE antibodies to sperm antigens were detected in the blood serum of 7 (17.5%) infertile patients. The maximum IgE level was 4 times higher than the threshold value for the women in the control group. There was no correlation with total IgE. Pearson's correlation coefficient was 0.024166.

Conclusions
According to the results of the study, it was found that up to 50% of women with IgE to sperm proteins noted a reaction already to the first contact with sperm, which suggests a possible cross-allergenic reaction. Probably, some women with sensitization to seminal fluid and spermatozoids were previously sensitized to cross-allergenic epitopes. Thus, cross-sections were established between “Can f 5” prostate kallikrein molecules of dog and PSA (prostate specific antigen). This issue deserves a separate scientific study. The established sensitization in 17.5% of women with infertility of inflammatory genesis to sperm proteins should be taken into account when choosing personalized approaches to the treatment of infertile couples. In addition, also should consider the presence of sensitization during IVF procedures.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Multi-site hospital as an efficient tool to mitigate the cesarean section rate: findings from a time-trend analysis in southern switzerland

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Context
As a consequence of the global increase of the abdominal surgery in obstetrics, policy and service provision recommend the promotion of strategies to decrease the rates of cesarean section (CS). Influence of several factors, including local geography, should be accounted in the strategic planning to reduce CSs.

Objective
To investigate the role of the healthcare model based on a multi-site hospital in the mitigation the rise of CS in southern Switzerland.

Methods
All deliveries occurred during a 9-year period (2010-18) in all settings were revised. Rates of modes of deliveries were calculated. Descriptive analysis and one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction for multiple comparisons were used to test the hypothesis of linear trend across the temporal study groups.

Patients
All women requiring assistance at delivery at the Obstetric Units of the Ente Ospedaliere Cantonale allocated in Lugano, Bellinzona, Mendrisio and Locarno (Ticino, Switzerland).

Main outcome measures
Trends in modes of delivery, dichotomized into vaginal deliveries (VD) and CS, according to the temporal criterion (Period I, 2010-12; Period II, 2013-15; Period III, 2016-18)

Results
A total of 16,286 women admitted for assistance at delivery were included in the analysis. A global rate of 76.6% of VD and 23.4% of CS was assessed. From Period I to Period III, a significant increase in VD rates (72.1 vs. 79.7%; $p<0.001$) was observed. By using ANOVA, a statistical linear tendency in reduction of CS birth rate from 27.9 to 20.3 per 100 births was calculated across the study periods ($p<0.001$). Successful decrease in CS rates were recorded in all intra-organizational settings of the multi-site hospital (from Period I to Period III in Lugano, from 35.5 to 28.5%; in Bellinzona, from 21.3 to 18.5%; in Mendrisio, from 28.0 to 17.9%; and in Locarno from 28.2 to 19.4%, ($p<0.001$), respectively)

Conclusions
Optimal healthcare systems should guarantee a prompt clinical assistance in presence of some geographical limiting factors, such as mountainous territory. A model based on a multi-site hospital represents an effective tool in achieving the international targets which are recommended in obstetrics.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Nutrition status determined by the body mass index (BMI) pregestational and obstetric complications in pregnant teens

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Context

Due to the high incidence and clinical, psychological and socioeconomic complications, pregnancy is considered as a phenomenon of interest.

Objective

Determine the nutritional status through the pregestational BMI and analyze the relate with the obstetric complications present in pregnant adolescents of the External Clinical of Gynecology and Obstetrics.

Material and Methods

Retrospective study of 1305 records of pregnant adolescents aged 12 to 19 years. Sociodemographic variables, anthropometric and laboratory data, and clinical characteristics were collected. Obstetric complications were classified into 10 categories: vaginal/urinary disorders, nutritional disorders, abnormalities of the fetus, physiology of the amniotic fluid, gastrointestinal/digestive disorders, hypertensive disorders, neurological disorders, pain, viral diseases and other complications. Descriptive and inferential statistics applied. Chi squared was used to contrast data

Results

We included 1305 records of pregnant adolescents. Mean age 17.35 ± 1.32 years, Mean initial gestation week 30.2 ± 7.3 week. 82% (n= 1048) was found at level No.3 of socioeconomic level, 94.2% (n = 1229) had no work and 67.4% (n = 879) attended high school. Mean height 1.57 ± 0.06 meters, mean pregestational weight 56.6 ± 13.8 kg. Regarding the pregestational nutritional status, 29.6% (n = 115) had low weight, 48.4% (n = 188) normal weight, 10.5% (n = 41) overweight and 11.3% (n = 44) obesity. The majority presented one or more obstetric complications 63.6% (n = 830), the most frequent obstetric complications were: physiology in the amniotic fluid 17.5% (n = 229), other complications 13.9% (n = 182), vaginal/urinary abnormalities 13.8% (n = 180) and abnormalities in the fetus 12.7% (n = 166).

Conclusions

There is a high prevalence of malnutrition (low weight, overweight and obesity), as well as a high incidence of complications in physiology of amniotic fluid, other complications, vaginal / urinary abnormalities and abnormalities in the fetus. It is recommended a nutritional intervention since the first prenatal visit, so that we can avoid the appearance of malnutrition and / or complications before and during the pregnant stage.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Considerations regarding the impact of vitamin D in pregnancy

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Context

Maternal-Fetal gestational pathology is one of the biggest challenges in the field of health at this moment. Preterm birth represents an important cause of neonatal morbidity and mortality, and a major public health problem. Despite the impact it has, preventing preterm births remains an unsolved issue. The best way to minimize the unfavorable prognosis of maternal-fetal pathologies is to prevent them. This is why it is necessary to determine the risk factors involved.

Objective

The current study is designed to determine the effects of vitamin D on pregnancy, starting from the idea that lower levels of vitamin D is thought to be related to premature birth.

Methods

This study is conceived relying upon the selected on-line published studies from international data bases. The analysis of research results is performed by assigning the pregnancies to one of two groups; the first group is a control one, with normal levels of vitamin D, the second group includes pregnant women who had a lower level of vitamin D. We also analyzed the results of the second group based on the therapy with vitamin D or the absence of it.

Results

The review shows that there is a strong relationship between the poor level of vitamin D levels during pregnancy and adverse outcomes. It was shown that maternal serum 25 (OH) vitamin D deficiency (<50 nmol/l) was associated with increased risk of preterm birth, and maternal oral supplementation with vitamin D during pregnancy can reduce the risk of preterm birth, but the right approach is still unclear. Several studies have linked vitamin D deficiency with preeclampsia, gestational diabetes mellitus, caesarean section, low birth weight, neonatal rickets, risk of neonatal hypocalcemia, asthma and type 1 diabetes. It was also shown that vitamin D supplements can reduce the risk of preeclampsia by 48%, preterm birth by 64% and low birth weight by 60% compared with no intervention or placebo. During this review, we could not find studies regarding the necessary supplementation of vitamin D in pregnancy related to the geographical belonging and the seasons of the year, therefore this could be a reason for the increased incidence of gestational and neonatal pathology.

Conclusions

As worldwide screening programs have not been yet initiated, the present research stands for a well-founded support to recommend checking the levels of 25 (OH) vitamin D during pregnancy, correlated with geographical belonging and seasons of the year.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Maternal folic acid intake and children with ventricular septal defect: cases and control

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Context

The most common malformations are congenital heart defects (CHD) and neural tube defects. Within the CHD, ventricular septal defect (VSD) is one of the most frequent malformations (1/1000 births). It has been reported that folic acid (FA) supplementation before and/or during pregnancy could reduce the risk of CHD. However, contradictory results have been observed. Regarding the dietary intake of FA, no associations have been observed with the risk of CHDs.

Objective

To determine if maternal dietary intake of folic acid is associated with the presence of VSD in children.

Methods

Pilot-exploratory, cross-sectional, observational, descriptive study. 69 mothers and their children were evaluated (17 cases and 52 controls). Mothers, dietary variables were collected through a food frequency questionnaire with FA and consumption of supplements with FA; clinics (presence of maternal diabetes mellitus, exposure to medications during pregnancy) and drug addiction (alcoholism). The presence of VSD and family background were determined from the children. Statistical analyzes were performed in the SPSSv.22 software (SPSS Inc.; Chicago, IL, USA).

Result(s)

58.8% of the cases were men and 41.2% women. A higher maternal age was observed in children with VSD but without significant differences (25.4±6.8 vs 21.88±4.4; p = 0.058). Maternal dietary intake of FA was similar in both groups (p=0.854), it was also reported that 100% of mothers with healthy children consumed FA supplements, in contrast to children with VSD, who 29.4% reported not to consume FA supplements, observing statistically significant differences (p=0.001).

Conclusions

Only the consumption of supplements with FA was different between cases and controls and although there was a tendency at an older age in mothers with children with VSD, but no significant differences were observed, in the same way as the presence of maternal diabetes, exposure to medications, occasional alcoholism or dietary intake of FA are related to the presence of VSD in children.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Onset of nausea and vomiting in pregnancy: a prospective cohort study

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Context
Nausea and vomiting (NVP) has been recognised as a feature of early pregnancy for well-over 2000 years. However, the precise date and characteristics of its onset have been more difficult to define. Most studies are retrospective and date pregnancy from last menstrual period (LMP), which is an inaccurate measure of pregnancy duration, so onset appears heterogeneous.

Objective
Determine the onset of NVP in early pregnancy.

Methods
Single cycle, prospective cohort study of women seeking to conceive. Women collected daily urine samples from preconception onwards. Pregnant volunteers began recording symptoms of NPV for each hour in the day in daily diaries from day 30 following LMP. LH and hCG were measured (AutoDELFIA). Ovulation was assigned as the day after LH surge. hCG rise >1mIU/ml was considered as day of implantation.

Patients
A total of 1443 women seeking to conceive were recruited. Inclusion criteria were ≥18 and regular menstrual cycles. Exclusion criteria were known infertility, current pregnancy and medical conditions that contra-indicated pregnancy. 1073 volunteers did not achieve a pregnancy in 1 month, 82 had pregnancy loss, and 288 successfully conceived. Diary data was available from 256 women.

Main outcome measure
Onset of NPV in relation to LMP and Ovulation.

Results
Almost all women (94%) had some symptoms of NPV, with 35% experiencing just nausea and 59% having nausea and vomiting. Women with more than one previous livebirth experienced significantly longer average hours of symptoms. Implantation mostly occurred across a 3 day window of day 8-10 with respect to ovulation (88% of volunteers). Whereas, timing of implantation was more varied when timing from LMP; 88% across an 11 day window of days 20-30. This demonstrates ovulation to be a superior reference for duration of pregnancy.
Onset of NPV was relatively consistent in relation to ovulation, with two thirds of women having first symptoms 11-20 days from ovulation (and only 5% suffering from symptoms earlier). Using LMP as a reference, 67% of women had onset between 26-40 days. Symptoms started slightly earlier for those with higher BMI, and slightly later for older women.

Conclusions
The vast majority of women experience symptoms of NPV, which start within a narrow time window when referenced from ovulation. This supports current theories that the aetiology of the condition is related to the emerging physiology at the fetal-maternal interface.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Prolongation of pregnancy with PROM in gestational age up to 28 weeks

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Preterm rupture of the membranes (PROM) complicates 3% of pregnancies up to 37 weeks of gestation, the most unfavorable outcomes are in case of PROM before 28 weeks. Currently, there is no clear data on the optimal latent period before the moment of PROM and gestational age at delivery.

The aim of this study was to analyze perinatal outcomes in case of prolongation of pregnancy complicated by PROM up to 28 weeks, depending on the duration of the anhydrous period. A retrospective analysis of 38 cases of PROM in a gestational period of less than 28 weeks was performed. The study was conducted in Rostov Regional "Perinatal Center".

Miscarriage was observed in almost every second woman — 47.4% (18). A history of spontaneous miscarriage and/or missed abortions was noted in 36.8% (14) cases, premature birth - in 15.8% (6), while PROM - in 7.9% (3). Every third pregnant woman had cervical insufficiency - 36.8% (14), while prolapsed fetal membranes preceded PROM in 13.2% (5) cases. Surgical cerclage was performed in 10.5% (4) of pregnant women with cervical insufficiency, 23.7% (9) of women had obstetric pessary. Expectant tactic in PROM was selected in case of satisfactory state of pregnant woman, the absence of clinical symptoms of chorioamnionitis and signs of fetal suffering. Chorioamnionitis was diagnosed in 55.3% (21) patients. The anhydrous period ranged from 2 to 600 hours (25 days) and averaged 118 hours (5 days). 38.6% (17) of women had cesarean section. In the structure of indications for cesarean section prevailed: a scar on the uterus after cesarean section, malpresentation, placental abruption.

Early neonatal death (up to 7 days) among children born after PROM up to 28 weeks was 447.4 ‰ (17), late neonatal death (up to 28 days) - 26.3 ‰ (1). 5 children died after 28 days of life. 15 children were discharged or transferred to other hospitals with a mass of more than 2000 grams. Perinatal outcomes were analyzed in dependence on the duration of the anhydrous period and birth weight. The correlation coefficient between survival and the duration of the anhydrous period was 0.246 (weak connection). However, between the survival rate and the weight of the newborn, the correlation coefficient was 0.737 (strong relationship).

Thus, extremely unfavorable perinatal outcomes in women with premature rupture of the membranes before 28 weeks are not significantly associated with the duration of the anhydrous period, but they correlate with body weight at birth.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Does nutritional status differs between ages in pregnancy women?

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Context
Maternal nutrition plays a significant role to ensure a healthy infant. The risk of poor pregnancy outcomes will increase and a nutritional intervention must be neccesary

Objective
To describe the nutritional status through Gestational BMI of pregnancy women in a tertiary teaching Hospital in Northeastern México.

Material and Methods
We recruited pregnancy patients from the outpatient gynecology and obstetrics clinic, ages 14 to 40 years. Nutritional status was evaluated with anthropometric measures: body weight and height. We calculated Body Mass Index (BMI). We classified the age population into adolescents (10 to 19 years) and adults (20 to 59 years). Descriptive and inferential statistics applied. Chi squared was used to contrast data. The BMI classification was determined using the tables elaborated by Atalah, Castillo y Castro (1997).

Results
We included 140 patients. Mean age 22.4 ± 5.6 years, The mean gestation week was 15.0 ± 4.4 week and mean weight of 61.2 ± 12.3 kg; most frequent age was adults (63.6%), followed by adolescents (36.4%). We found that 38.8% had overweight, 34.7% normal weight and 26.4% underweight. About the trimester, 65.7% were in second trimester and 34.3% first trimester.
When comparing nutritional status between ages, we found that adults had higher values of overweight than adolescents (76.6% vs 23.4%; rho=0.246; p=0.006).

Conclusions
There is a higher prevalence of obesity in the adult population compared to adolescents, despite the fact that the adolescent population is considered as a population at risk during pregnancy. It is necessary more research on this field, but a nutritional intervention since the first prenatal visit to prevent obstetrics complications.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

Secretory leukocyte protease inhibitor as a key regulator of cervical remodeling in preterm labor and term delivery

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Objective

Drastic change in tissue property, so called cervical remodeling, occurs in the uterine cervix at peripartum period. The deterioration of this system can induce pathological pregnancy such as preterm birth. Secretory leukocyte protease inhibitor (SLPI) is a multifunctional peptide which is secreted at mucosal epithelium. With its anti-inflammatory and anti-protease capacity, SLPI is involved in wide spectrum of physiological and pathological processes. In this study, we aimed to explore the association of SLPI actions with cervical remodeling.

Methods

This study was conducted under approval of our institutional ethics committee. Cervical cells were collected from the women at distinctive stages of healthy pregnancy and the women complicated with threatened preterm labor. In the cervical cell samples, gestational stage-specific shift of SLPI mRNA expression and its difference between healthy and complicated pregnancy were analyzed using real-time PCR. Cervical mucus samples were collected from the women at term pregnancy. SLPI concentration in the mucus samples were measured by ELISA and its correlation to cervical maturation status and the days to delivery were evaluated.

Results

Progressive elevation of cervical SLPI mRNA expression was detected and the peak of the expression was observed at postpartum. Compared with normal pregnant women, SLPI mRNA expression was enhaned in the women with threatened preterm labor, especially in the women finally ending in preterm birth. Remarkable increase in SLPI in the cervical cells was observed in the final month of human pregnancy. Positive correlation was confirmed between SLPI concentration in cervical mucus and the period to delivery ($R=0.37$, $p<0.01$). There was no correlation between SLPI and Bishop's score, an index for cervical maturation determined by pelvic manual examination.

Conclusions

Our findings suggest that gestational stage-specific functions of SLPI is key to successful regulation of cervical remodeling. Considering that anti-inflammatory and anti-protease capacities previously reported in SLPI, the detected elevation of cervical SLPI expression prior to delivery and at postpartum might be a suppressive counter action to inflammation and protease activities driving cervical maturation. The observations in this study propose that cervical SLPI can be a biomarker to predict the timing of delivery.

Pregnancy: lifestyle, obesity, pre-term labour and caesarean section

A prospective pilot study comparing incidence and characteristics of cesarean scar defects after uterine closure by double-layer barbed or smooth suture

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Context
Late sequelae of a cesarean section related to a uterine scar defects include gynecological symptoms and obstetric complications.

Objective
This study aims to evaluate the incidence and characteristics of cesarean scar defects after uterine closure by double-layer barbed suture.

Methods
Women who underwent elective cesarean section at ≥ 38 weeks of gestation at our institution were included in this prospective comparative study. Exclusion criteria were a previous cesarean section or uterine surgery. Low transverse hysterotomy was closed either by a double-layer unidirectional barbed suture or by a conventional double-layer smooth suture. The choice of the suture was based on the preference of the surgeon. The first uterine layer was close by continuous unlocked suture, including the endometrial layer; the second uterine layer by continuous unlocked suture imbricating the first. A saline contrast hysterosonography (SCHS) was performed six weeks, 6 and 12 months after cesarean section. A niche was defined as an indentation at the site of a cesarean section scar with a depth of at least 2 mm in accord with the modified Delphi procedure. Niche depth and length, residual myometrial thickness in the uterine sagittal plane were calculated. Postoperative complications were collected.

Results
Among 161 women, 64 patients underwent uterine closure by barbed suture and 97 by smooth suture. Six weeks after cesarean section, at SCHC the residual myometrium thickness (± SD) was significantly higher in the barbed suture (4.8±1.3 mm) than in the smooth suture group (4.0±1.3 mm; p<0.001). After 6 months, there was a lower incidence of niche in the barbed suture (18.5%, n=10/54) than smooth suture group (33.7%, n=29/86; p=0.043). The incidence of complex niche was not different between the two suture groups (7.4%, n=4/54 vs 7.0%, n=6/86; p=0.672). The mean (± SD) niche depth was 2.4±1.2 mm in the barbed suture and 3.6±0.5 mm smooth suture group (p=0.006); the mean length (± SD) was 2.0±1.3 mm and 2.8±1.1 mm, respectively (p=0.018). After 12 months, there was a significantly lower incidence of niche in the barbed suture group (16.6%, n=7/42 vs 31.9%, n=22/69; p=0.046). The incidence of postoperative complications was similar between the two groups.

Conclusions
Uterine closure by double-layer barbed suture during cesarean section may be characterized by a low incidence of scar niche formation and reduced size of the niche in women who have developed them.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

Is preeclampsia phenotype different in pregnancy with gestational diabetes?

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Context
High prevalence of gestational diabetes (GD) and social importance of preeclampsia (PE) due to massive perinatal morbidity and mortality as well as high rate of preeclampsia in GD pregnancy defines the need to study the characteristics of pregnancy course in these women to develop the prevention and management of pregnancy complication.

Objective
To study clinical and laboratory features of PE in GD pregnancy

Patients
According to the inclusion criteria 112 pregnant women were enrolled in the prospective cohort study after 24 gestational week: with GD+PE (n=24); with PE (n=22); with GD (n=37), without studied pregnancy complications (n=37). All patients with GD were treated properly according to the national guidelines. Most of the women (73-74%) had good glycemic control (not different between groups: p=0.8).

Main outcome measures
Serum levels of PIGF and sFLT-1, pregnancy course and labour using medical history.

Results
Severe preeclampsia was present more often (p=0.0014) in PE group (59%, n=13) comparing to the GDM+PE group (13%, n=3). Elective preterm labour occured more often in PE group comparing to other groups (PE: 23%, n=5; GDM+PE: 9%, n=2; p<0.0001) that is in line with the severity of this complication in PE group. The rate of preterm labour did not differ between GDM+PE and the group without studied pregnancy complications. The mean fasting glucose is higher in GDM group comparing to GDM+PE group (p=0.01). GDM+PE group characterized by fasting hyperglycemia episodes and base insulin regimen, while GDM group - by postprandial glucose peaks and bolus insulin regimen. Women with GDM+PE were notable for the high prepregnancy BMI (29,00±6,58 kg/m^2) and family history of DM was typical for women in GDM group (59%, n=19). sFLT-1/PIGF level did not differ between GDM+PE group, GDM and controls and was lower comparing to the PE group (p<0.0001). PIGF level was not different in GDM+PE and GDM group, but lower comparing to controls.

Conclusions
Our study showed that PE in women with adequately treated GDM is more benign than isolated PE taking into account both clinical and laboratory signs. Given that obesity appears to be one of the most important risk factor for both pregnancy complications. Present study data adding the existing literature position allow to suppose that initial carbohydrate disorders play limiting protective role in vicious PE cycle due to the angiogenesis stimulation.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

New method for differential diagnosis of PE and superimposed PE

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Context

Preeclampsia (PE) is a pregnancy complication with high maternal and perinatal morbidity and mortality. PE is a multifactorial complication that is also confirmed with various PE phenotypes different in severity and prognosis. Effective differential diagnosis of isolated PE and superimposed PE (including masked and undiagnosed chronic hypertension (HT)) is highly required in pregnancies with high blood pressure and absence of multiple organ failure. The distinction of phenotypes plays an important role in antihypertensive therapy as well as in terms of safe pregnancy prolongation that is often the leading factor in neonatal morbidity.

Objective

To develop the algorithm to distinguish PE and superimposed PE in pregnancies with high blood pressure and absence of multiple organ failure.

Methods

Standard clinical and laboratory signs of PE, serum lipids, arterial stiffness markers: augmentation index (AI) standardized to 75 per minute heart rate and pulse wave velocity (PWV) (using automated oscillometry, BPLab with "Vasotens" program; ESH-2001 certificate № CE 576857) were assessed. All together we used 29 characteristics.

Main statistical method

Linear model of discriminative analysis.

Patients

According to the inclusion criteria 83 pregnant women were enrolled in the prospective cohort study: 48 with PE without chronic hypertension anamnesis and 35 – with superimposed PE diagnosed according Russian and European guidelines.

Main outcome measure

Sensitivity and specificity of the method.

Results

The significant characteristics for differential diagnosis were PWV and AI additionally to maximal systolic blood pressure (SBP) during hospital stay and serum aspartate aminotransferase. As a result classification function was written and the decision can be made with calculation by formulas: S1=0,6505×SBPmax+5,5947×PWV+17,7756×Log AST–0,4911×AI–90,5509 S2=0,744× SBPmax +6,614× PWV +20,27× Log AST –0,583× AI –121,244. Dianostics criteria: in case of S1>S2 isolated PE is diagnosed, S2>S1 – superimposed PE. Sensitivity of the decision rule was 89%, specificity – 91%, classification accuracy – 87%.
The method was approved by Federal service of intellectual ownership (application № 2019130693/04(060289)).

Conclusion

In case of PE signs with high HT and absence of multiple organ failure as well as lack of the data including chronic hypertension anamnesis new method for differential diagnostics of superimposed PE might be offered for further research.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

In vitro evaluation of drug association between crude *allium sativum* l. (garlic) extract and antibiotics against resistant and sensible *Escherichia coli* strains

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Context

Allium sativum (garlic) is utilized in traditional medicine for several therapeutic benefits, including antimicrobial activity, proven in scientific studies. Escherichia coli mainly causes urinary tract infections, also responsible for important obstetric complications such as premature birth, miscarriage, and sepsis. Synergistic actions between antibiotics and garlic could be of clinical relevance, reducing antibiotic dose, adverse effects and treatment length.

Objective

In vitro evaluation of the susceptibility of E. coli strains to the crude extract of A. sativum (CEA), and the impacts of the association between the CEA and antibiotics (Ceftriaxone, Cephalotin, Ciprofloxacin, Levofloxacin, Gentamicin, Meropenem, and Imipenem) in the growth inhibition of resistant and sensible E. coli strains.

Methods

E. coli strains were grown on Müeller-Hinton agar following the Kirby-Bauer method for 48 hours in a macrodilution susceptibility test for antibiotics; A. sativum crude extract (CEA); and the association of each antibiotic and the CEA. The inhibition zone diameters of the antimicrobials were measured following the CLSI parameters, sorting strains in groups of resistant and sensible strains. The antimicrobials' performances were compared by the Wilcoxon test.

Patient

None

Intervention

None

Main outcome measures

Halos of inhibition in millimeters
Group (Antibiotic Median /CI95%; Antibiotic + CEA Median / CI95%)
Cephalotin Resistant Group (0.00 /0.95- 5.18; 21.00/ 19.47- 21.69) n=31
Levofloxacin Resistant Group (0.00/ 0.27- 1.52; 21.00/ 19.71- 21.73) n=32

Results

Against sensible E. coli strains, the association of CEA with all antibiotics disks displayed superior performance when compared to the isolated antibiotics and CEA disks ($p<0.05$). Against resistant strains, the association of CEA with Ciprofloxacin, Levofloxacin, Ceftriaxone, and Cephalotin disks displayed superior performance when compared to the isolated antibiotics and CEA disks ($p<0.05$). Remarkably, the associations between the CEA and the Cephalotin and Levofloxacin disks were able to create a halo with a confidence interval above the threshold to consider the bacteria sensible to the antibiotic, which could indicate the overcoming of antibiotic resistance.

Conclusions

Against the sensible strains of E. coli, all antibiotics displayed synergism with the CEA. Against the resistant strains, Ciprofloxacin, Levofloxacin, Ceftriaxone, and Cephalotin displayed synergism with the CEA.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

The features of hemodynamic supply of pregnancy during gestational endotheliopathy

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Background

There is reason to believe that endothelium acts as one of the most important mechanisms for resolving such a conflict of regulation, which ensures the "escape" of the vessels of the fetoplacental complex from the systemic vasoconstrictor influences at the organ-tissue level. The purpose of this study is to investigate whether gestational endotheliopathy, as assessed by hemodynamic supply features of pregnancy, in women with perinatal pathology is associated with an increased risk of preeclampsia, placental dysfunction, preterm births.

Materials and methods

In accordance with the purpose of the study, 213 pregnant women were examined. Group I included 108 women aged 18-27 years, whose pregnancy proceeded physiologically. Group II was made up of 105 pregnant women (aged 19-26 years) with obstetric pathology on the background of a Gestational endotheliopathy. The control group consisted of 117 healthy non-pregnant women aged 19-26 years. Endotheliopathy was diagnosed using tests for microalbuminuria and endothelium-dependent vasodilation (ESVD).

Results

In women in first group, with fundamentally the same direction of changes, a significant increase in the share of type III blood circulation (up to 36%) was observed only in the 3rd trimester. A sign of a divided optimization of blood circulation in women with physiologic pregnancy in the 1st trimester there was a significant increase in pregnant women with optimal characteristics in the entire set of hemodynamic parameters - from 58% in control group to 74% ($p < 0.05$). In this case, unlike pregnant women of group II, there were completely no patients with suboptimal levels of total totality of hemodynamic parameters. In the III group, the proportion of women with this condition was 8%, and in the group II with - 15%. Accordingly, the more intense state of blood circulation in pregnant women of group II by the 3rd trimester significantly and expressively decreased the proportion of optimal conditions - from 58% to 8% ($p < 0.05$). At the same time, the share of non-optimal and transitional states increased from 8% and 34% in the control, respectively, to 29% ($p < 0.05$) and 63% ($p < 0.05$).

Conclusions

The data obtained make it possible to accept hypertensive syndrome as the hemodynamic equivalent of endothelial activity in based on the mechanism of "escaping" vessels of autonomous (tissue, organ, regional) regulation of arterial blood flow and redistributive regulation of blood circulation.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

How to improve placental perfusion and umbilical artery vascular resistance in second trimester of singleton pregnancy?

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Objective

The aim of our study was to analyze the therapeutic effects of pravastatin /L-arginine therapy on improvement of placental perfusion and decrease of umbilical artery vascular resistance in singleton pregnancies with increased umbilical artery pulsatility index for gestational age.

Methods

In this study 12 pregnant patients, with isolated increased umbilical vascular resistance and normal uterine artery doppler findings, were included. Pravastatin 40mg / L-arginine 1500mg per day, was administered when umbilical artery pulsatility index was measured above limits for gestational age. Patients were scanned in 2-4 week interval to follow up changes in vascular resistance in umbilical artery.

Results

12 pregnant patients had singleton pregnancy. Median gestational age, when increased umbilical vascular resistance was detected and therapy introduced, was 23 weeks (18-30 weeks). Therapy was introduced when PI values in the umbilical artery were above normal limits for gestational age. Improvement of umbilical artery PI values was confirmed in 11 patients. Median period of improvement in umbilical circulation was 2 weeks. Fetal cerebral, aortal, renal circulation and uterine arteries vascular resistance remained normal throughout pregnancy. Median gestational age at delivery was 40 weeks. Median 1/5 min Agar score was 9/10. 11 neonates were born without signs of intrauterine asphyxia. Mean neonatal weight was 3331±389g. In one patient, who had normal umbilical artery vascular resistance until 30th week, therapy was introduced after significant rise of umbilical artery PI to 1.5. Fetal condition was intensively monitored and umbilical artery PI values continued to rise until 35 weeks when AEDV occurred. Fetal cerebral circulation showed initial blood redistribution towards central nervous system. Pregnancy was carefully monitored and, when cardiotocographic monitoring indicated imminent asphyxia, cesarean section was performed at 35 weeks of pregnancy. Neonatal weight was 2400g, Apgar score was7/8. Histopathological examination of the placenta confirmed placental infarction.

Conclusion

In patients with isolated increased umbilical artery vascular resistance, increased placental perfusion and decreased vascular resistance in umbilical arteries was achieved after administration of Pravastatin 40mg/L-arginine1500mg daily. Administration of this therapy reduced the incidence of premature delivery due to fetal asphyxia.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

Quantitative determination of the content sFlt1 protein in pregnant women with preeclampsia

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Objective

Early detection of patients with an increased risk of preeclampsia is one of the most important tasks of modern obstetrics. Currently, as a result of many years of research, several potential markers can be distinguished that, independently or in combination with each other, can be used as prediction factors for preeclampsia. The purpose of our study: Prediction of pregnancy complications by preeclampsia based on the study of sFlt1 protein content.

Materials and methods

We conducted a study of the concentration of sFlt1 protein in women with physiological pregnancy and in pregnant women with mild and severe preeclampsia. The control group consisted of 30 pregnant women with a physiological course of the gestational period, the first group included 20 pregnant women with mild preeclampsia, and the second group included 22 pregnant women with severe preeclampsia.

Results

During physiological pregnancy, the content of sFlt1 was 0.16 ± 1.2 ng / ml, with preeclampsia there was a significant increase in the concentration of soluble sFlt1 - 1.59 ± 3.5 ng / ml with mild preeclampsia, 8.79 ± 4.9 ng / ml for severe preeclampsia. With increasing severity of preeclampsia, the concentration of sFlt1 protein rises to 8.81 ± 4.9 ng / ml in severe preeclampsia. In pregnant women with severe preeclampsia, in parallel with a rise in blood pressure and proteinuria, the concentration of sFlt1 protein in the blood increases.

The results of the study indicate that in the III trimester of pregnant women with a physiological course of pregnancy, as well as with preeclampsia of varying severity, there are changes in the level of angiogenesis factor. In the physiological course of pregnancy in the III trimester, a regular decrease in the activity of the angiogenesis factor occurs, since the sFlt1 protein is an inhibitor of angiogenic factors, the synthesis of which is suppressed.

An increase in the concentration of sFlt1 protein leads to a deficiency of angiogenesis factors, which causes endothelial dysfunction of vital organs and contributes to aggravation of the severity of preeclampsia. The concentration of angiogenesis factors depends on the severity of preeclampsia. The maximum increase in sFlt1 protein concentration is observed with severe preeclampsia.

Conclusions

The results of the study showed that determining the level of angiogenic factor sFlt1 protein in preeclampsia of varying severity is important for predicting pregnancy complications.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

Prognostic significance of critical disorders of feto-placental blood flow in pregnant women with intrauterine growth restriction

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Intrauterine growth restriction (IUGR) is a pregnancy complication in which the fetus doesn't reach its anthropometric indicators that are programmed with an individual genetic code. The aim of this study was to analyze the indicators of fetoplacental hemodynamics (blood flow in the arteries of the umbilical cord and ductus venosus) and assess the effect of fetoplacental blood flow on the outcome for the newborn.

A retrospective analysis of 138 births from 2017 to 2019 was carried out on the basis of Rostov Regional "Perinatal Centre". The study included women with IUGR fetuses, with birthweight less than 2000 grams. Diagnose of the IUGR was based on ultrasound and dopplerometric indicators using percentile curves. Statistical processing of the results was carried out using the statistical criteria of Fisher and Mann-Whitney. First group included women, whose newborns died within 28 days after birth (n = 22), the second group included women with neonatal survivors (n = 116). Mean gestational age at delivery was 32.4 ± 2.5 weeks of pregnancy. The groups were comparable in gestational age at delivery, age of women, initial BMI, concomitant pathology and obstetric-gynecological history, as well as frequency of cesarean section. In most cases pregnancy was terminated due to severe preeclampsia or decompensation of fetus hemodynamics.

The number of women without fetal-placental blood flow disorders or with moderate disorders without critical values were comparable in the analyzed groups. Number of women with critical fetoplacental blood flow disorders was statistically significant higher ($p < 0.0001$) in the group where the newborns didn't survive - 45.5% (10), compared with the group with surviving children – 17.2% (20). Thus, the mortality rate among children with critical blood flow disorders was 33.3%, which is statistically significantly ($p < 0.01$) higher than in children without critical disorders (11.1%), RR 3.0, 95% CI [1.3-6.62]. Zero or reverse end-diastolic blood flow in the umbilical artery predominated in all cases of critical disorders of fetoplacental hemodynamics. disturbance in ductus venosus (retrograde blood flow) was more frequent ($p > 0.05$) in the first group.

Thus, critical disturbance in fetoplacental hemodynamics was statistically more frequent in group of women, whose children died in first 28 days of life.

Pregnancy: hypertension, pre-eclampsia, intrauterine growth and infectious diseases

The role of a gluten free diet and antibiotic treatment on the prevention of fetal growth restriction, preterm birth, to increase the placental blood flow

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Liberi professionisti

Context

In industrialized countries, about four-fifths of low birth-weight infants are born preterm and a fifth of these pre-term births are due to intrauterine growth restriction(IUGR).. The etiology of IUGR remains undetermined, but several risk factors for the conditions have been identified.
Intrauterine growth restriction (IUGR) is defined as fetal growth less than the normal growth potential of a specific infant because of genetic or environmental factors. Various maternal, placental, neonatal, environmental and genetic factors are contributing to the preponderance of IUGR infants.

Objective

In this review we would like to present the possible etiology related to maternal, fetal and placental causes; short term and long term neurodevelopmental outcomes, and evidence based preventive interventions effective in reducing the IUGR burden.
The main aim of this study is to analyze that treatment with combined gluten free diet and antibiotic therapy increases the placental blood flow and particularly improves abnormal uterine artery doppler velocimetry in high risk pregnancy. Such pathological changes are considered to be responsible for very high utero-placental resistance, leading to blood flow insufficiency in pre-eclampsia or intrauterine growth retardation. It is possible that Gluten free diet and antibiotic administration could have a role on anticoagulant, vasomotor and inflammatory effects of the endothelium altered by the bacterial inflammation caused by celiac disease.

Method

We examined one hundred and seventy pregnant patients afferent to our private practice starting from the 28th week of amenorrhea with umbilical artery flow Doppler alterations with PI values> 2 SD by gestational period, with fetuses affected by IUGR and without obvious maternal pathology.
We subjected patients to antibiotic therapy with diaminocillin 1 gram tablets every 12 hours for 6-12 days and with low carb and gluten-free diet. We monitored patients: control of clinical and blood chemistry parameters, weekly ultrasound assessment of fetal growth and umbilical artery Doppler flowmetry.

Results

The diet and the antibiotic therapy have determined a rapids resolution of the parameters already altered of the velocimetria Doppler and improve of fetal growth in all the patients in the following week to the therapy.

Conclusion

The data above reported they propose the objective of a therapy of the IUGR in pregnancy to the goals of the prolongation of the pregnancy, necessary to reduce the connected risks to the fetal prematurity and the prospect of an outpatient IUGR management.

Menopause

Hormone replacement therapy in cancer survivors

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Continuous and rapid advances in oncology leads to increasing survival of oncological patients. Moreover, it is recognized that as a consequence of treatments, women experience premature ovarian insufficiency with vasomotor symptoms, long term negative cardiovascular and skeletal effect and therefore a poor quality of life too.

Objective

To evaluate the effects of Hormone Replacement Therapy (HRT) on hot flashes in cancer survivors. as well as the impact HRT has on quality of life.

Methods

Observational and analytical study of a retrospective cohort using the database of the Climacteric Section between July 2010 and november 2018.

40 women under 50 with a history of a non-hormone dependent cancer presenting hot flashes were included in the study. The patients were evaluated at a basal point before beginning HRT and during their follow-up of up to 24 months.

Hot flashes were evaluated through a Hot Flashes Score which calculated the average of hot flashes the patients recorded daily within one week. For the assessment of quality of life, the women were asked to fill in the Cervantes Scale. In the descriptive analysis, the quantitative variables are conveyed through the median and the interquartile range 25-75 (RIC25-75). The statistical significance was considered to be below 0,0005. The analysis was made with the R software.

Results

Data was collected from 40 women with a mean age of 35 (RIC25-75 33 – 41). 62.5% had a history of cervical cancer, 33.3% of ovarian cancer and 4.17% of other cancers. 58.3% of the patients were prescribed with Tibolone, 41.7% with estrogen with or without progesterone.

29 of the 40 women filled out the hot flashes score and 16 out of 40 the Cervantes Scale. Those were included in the analysis.

In the variables analysed, the median of the basal score was 2 whereas the median during the follow up was 0.28 which shows that HRT improved significantly the presence of hot flashes (RIC25-75 - 4 a 0). When quality of life was assessed through the Cervantes Scale, the median at the basal point was 46 (RIC25-75 19-73) whilst at the follow up it was 47 (RIC25-75 22-59). Despite the fact that there was no statistically significant difference (p = 0,3173), the tendency suggests an improvement

Conclusion

According to the results found in this study, HRT has a positive effect on managing hot flushes and on the quality of life and could be considered as an option. The focus should be on striving to improve their quality of life.

Menopause

Safety evaluation of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy: a prospective observational study

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Context

The use of fractional CO2 lasers emerged as viable alternative to successfully treat Genitourinary syndrome of menopause (GSM)

Objectives

To evaluate the safety and satisfaction related to fractional CO2 laser for the treatment of vulvo-vaginal atrophy (VVA) in postmenopausal patients.

Patients and methods

Fifty- three patients affected by VVA were considered for the study. All women were treated by using Lumenis AcuPulse DUO (Lumenis, Yokneam, Israel) in fractionated mode with a 28 mm probe FemTouch™ .

Intervention

pain during different steps of procedures was evaluated as follow: introduction, rotation and extraction of probe and laser impulse' s transmission using 7- point Likert scale. The occurrence of side effects was prospectively evaluated: at the end of the procedure, before 30 days and after 30 days after the first treatment. Participant satisfaction was measured on 7- point Likert scale.

Main outcome measure and results

No severe complications occurred after a median follow-up of six months. One patient (1.9 %) reported dizziness immediately after treatment, which was completely solved within 15 minutes. A minor bleeding occurred related with tip introduction and rotation. One patient (1.9 %) aborted the procedure for discomfort to probe introduction. Two patients (3.7%) reported symptoms of dysuria within 7 days from procedures. The mean overall pain score at first treatment, evaluated with seven-level Likert scale was 3.57 ± 1.50. The mean pain score related to probe introduction and rotation was 3.13 ± 1,37 and 2.32 ± 1,08 whereas pain related to extraction and laser impulse' s transmission was 1.23 ± 0,27 and 1.13 ± 0,37 respectively. The mean difference between overall pain score (1.27; CI 95% 0.83-1.71, p<0.001), pain score related to probe introduction (0.54; CI 95% 0.18- 0.90, p:0.001) and probe rotation (0.46; CI 95% 0.12- 0.90, p:0.003) was statistically significant reduced between the first and third treatment. Overall the satisfaction related to the procedure was high: 89.7% of patients would highly recommend the procedure and 94.9% of patients would be ready to repeat the procedure to keep results.

Conclusion

Fractional CO2 laser for treatment of VVAi s a safe therapeutic option. No severe complications occurred. A minority of patients reports mild complications solved without need of any further treatment. Overall patients were highly satisfied, and they would repeat laser treatment.

Menopause

Rebound-associated vertebral fractures after stopping denosumab: report of four cases

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Context

Denosumab is a potent reversible antiresorptive agent, which increases bone mineral density (BMD) and reduces the risk of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis. After discontinuation of denosumab, bone turnover markers (BTMs) transiently rebound above baseline levels. BMD and fracture risk return to baseline, but recent clinical trial data and case reports suggest a small but significant transiently increased risk for multiple vertebral fractures upon denosumab discontinuation. This has lent further credence to the notion of so-called rebound-associated vertebral fractures (RAVFs) after denosumab discontinuation.

Methods

We searched for cases of RAVFs in the records of the Center for Metabolic Bone Diseases (UZ Leuven).

Results

Four cases of RAVFs after discontinuation of long-term denosumab treatment were found. All were bisphosphonate-naïve postmenopausal women presenting with back pain 8-10 months after the last denosumab injection. All suffered multiple vertebral fractures with an average of 4 (range 2-6) vertebrae fractured. Two patients underwent vertebroplasty and sustained additional vertebral fractures. In three of the patients we have data on BTMs at the moment of presentation with RAVFs, all showing elevated BTMs.

Conclusion

Based on current knowledge, it is recommended not to stop denosumab without considering alternative treatments in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk. Moreover, vertebroplasty seems an unsuccessful approach for RAVFs and should be avoided in these patients. There is an urgent need to identify patient groups at risk of RAVFs and to design optimal management protocols for denosumab discontinuation.

Menopause

Irisin deletion induce glucose/lipid metabolic derangement and deteriorated bone loss in menopause

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Irisin is a product of fibronectin type III domain-containing protein (Fndc5), and involved in the regulation of adipokines secretion and differentiation of osteoblasts and osteoclasts. In this vivo study, we aimed to determine if irisin deletion could affect glucose/lipid metabolism and bone metabolism. Here, we knockout Fndc5 gene to generate irisin-deficient (KO) mice. Female wild-type (WT) and KO mice were fed with standard diet for 48 weeks. Effects of irisin deletion on obesity, glucose tolerance, insulin sensitivity and serum inflammation were determined in mice. Besides, the continuously measurement of bone microarchitecture in mice from young (12 weeks) to menopause (48 weeks) were performed. Then, we measured bone strengthen and serum levels of bone parameters (osteocalcin (OCN), and Tartrate-resistant acid phosphatase (TRAP)) after mice scarified. Irisin deletion induced abdominal fat accumulation, poor glucose tolerance and insulin resistance. KO mice were hyperlipidemia, with lower HDL level, and higher LDL level. Decreasing bone strengthen and bone mass in KO mice, indicated that irisin deletion aggravated bone loss in menopause. Pro-inflammatory cytokines in serum, like IL-6 and TNF-a were increased in KO mice. We found that irisin deletion caused glucose/lipid metabolic derangement and deteriorate bone loss in menopause. Further studies are needed to confirm these initial observations and to explore the mechanisms underlying the effects of irisin on the glucose/lipid and bone metabolism.

Menopause

Comparison of MHT treatments based on estradiol or estetrol on breast cancer: a preclinical study

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Context
The fear of the possible increase of breast cancer risk due to the use of menopause hormone treatment (MHT) led an increasing number of women to avoid the use of these treatments. This is a major concern for health and quality of life of women, to gynecologists and to the scientific community. In addition, several observations among which the stronger association with MHT use for patient with estrogen receptor-positive (ER+) breast cancer than with ER- one support that the promotion of breast cancer by MHT is mainly driven by an acceleration of breast cancer growth than by the induction of breast carcinogenesis.

Objective
The aim of this preclinical study was to compare the impact of several MHT treatments based on Estradiol (E2) or on Estetrol (E4), combined or not to progestogens, on breast cancer growth.

Results
First, to model human MHT treatment in mice, we had to define the dose and the route of administration of the steroids that were used. The doses were defined based on current FDA guidance for MHT treatments with E2 and progesterone (P4) or on clinical studies for E4. Then, the impact of these MHT treatments was evaluated in three different models of breast cancer. We used the transgenic polyoma middle T oncogene-induced (MMTV-PyMT) mice. These mice develop breast tumors that recapitulates the different steps observed during the carcinogenesis of human luminal-like hormone-dependent breast cancer. It also allows the assessment of metastasis dissemination to the lung. To assess the impact of MHT treatments on human breast adenocarcinoma tumors, we used human ER+ adenocarcinoma MCF7 cell line xenograft to immunodefiscient mice. Finally, patient derived xenografts (PDX) are currently the most powerful tool for understanding breast cancer characteristics and for predicting drug potency. PDX consists in the direct transfer of human tumors into immunodeficient mice. PDX models maintain the original features of patient tumors and reflect drug sensitivity. It allows the treatment of human breast tumors in *in vivo* conditions since the tumor is submitted to blood circulating levels of the drug tested.

Conclusions
We compared the impact of several MHT treatments based on E2 or E4 and combined or not to progestogens. By combining genetically engineered mouse models, human cell line xenografts and PDX, this study presents a high predictive value for assessing the impact of new MHT treatments on breast cancer.

Menopause

Improvement of vulvo-vaginal atrophy in postmenopausal women who receive pharmacological treatment with ospemifene in clinical practice: the AYSEX study (real world data study)

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Objective
To assess the improvement in vulvovaginal atrophy (VVA) of 100 postmenopausal women treated with ospemifene 60 mg/day under conditions of routine clinical practice after 3 months of follow-up. Other objectives were to assess changes in sexual function and quality of life, and evaluate satisfaction with treatment and adverse effects reported throughout the Real World Data study.

Method
The AYSEX trial is a Spanish prospective, unicentric observational study in which five gynecologists recruited postmenopausal woman with VVA in routine clinical practice treated with ospemifene 60 mg/day. This study includes different endpoints that will be measured at 3, 6, and 12 months, being the focus of this paper the 3 and 6 months analysis. Vaginal health (using a Vaginal Health Index), sexual health (using Female Sexual Function survey), severity of symptoms, quality of life, and satisfaction with treatment were assessed at baseline and after three months. The changes in the resorption bone marker CTX were analized at base line and after sin months. And the endometrial safety was evaluated at base line and after six months with the treatment with vaginal ultrasound.

Results
A total of 100 postmenopausal women cytologically and clinically diagnosed with VVA were included in the study, with a median age of 58.0 years. After three months of treatment with ospemifene, Vaginal Health Index improved and vaginal pH decreased significantly ($p < 0.0001$). In addition, a significant improvement was observed in sexual function and quality of life, and a significant decrease was observed in the severity of the more bothersome symptoms of VVA, such as dyspareunia and vaginal dryness. Patients reported to be satisfied with the treatment. The resorption bone marker CTX decreased from baseline till the 6 month after treatment, and the endometrium thickness didnt change after 6 months with ospemifene.

Conclusions
This study in daily clinical practice conditions confirms the results previously reported by randomized controlled trials, including (as) a significant improvement in VVA, and sexual function,; a significant reduction in the severity of the more burden symptoms, improvement in the perception of their quality of life, and satisfaction with the treatment and with the time that takes to the drug to make effect. Theres also a bone positive effect of this SERM, withouth changes in the endometrium.

Menopause

Changes in intervertebral discs with the menopause and HRT

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Context
Vertebral fracture is a very common osteoporotic fracture, the cause of which can be mostly attributed to reduced bone density. Intervertebral discs are an integral part of the skeleton and are important in function. Therefore, reduced intervertebral disc height might predispose to fractures.

Objective
To investigate the relationship between intervertebral disc heights of pre-and post-menopausal women and between the inter-vertebral disc heights of post-menopausal women on no treatment and those on various menopausal treatments including HRT.

Methods
A Cross Sectional Study was done by recruiting women from a large bone densitometry registry.

Patients
A cohort of 1080 patients was analysed.

Interventions
These were divided into categories according to whether they were pre-menopausal, untreated post-menopausal women or women on various post-menopausal treatments including HRT.

Main outcome measures
Three inter-vertebral disc heights were measured between [T12 and L1 (D1), L1 and L2 (D2) and L2 and L3 (D3)].

Results
HRT women had no significant changes compared to pre-menopausal women but highly significant improvement compared with strontium ranelate and particularly to women on bisphosphonates who had the lowest highly significant reduction in intervertebral disc height.
In addition there was a significant reduction in disc height in pre-menopausal women with age which accelerated in the immediate menopausal period (51-60) years. This was seen in every disc analysed.
When disc heights were compared to T-scores, those women who were osteopenic and osteoporotic had lower disc heights than women with normal T-scores.

Conclusions
Inter-vertebral disc heights present a new variable that impacts on bone integrity and incidence of osteoporotic bone fractures. Inter-vertebral discs are susceptible to osteoporosis at the time of the menopause just like other connective tissues including bone and skin. It is suggested that not all anti-osteoporotic agents have the same effect on inter-vertebral disc integrity and this might have to be borne in mind when considering the most suitable treatment according to the individual's needs.

Menopause

Body composition in patients with rheumatoid arthritis

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Context

Nowadays in the field of syndromes and diseases associated with age, scientists focus especial attention on the problem of sarcopenia, which combines an increased risk of falls, deterioration of life quality, impaired functional activity, reduced life expectancy and increased mortality of patients.

The aim of this study was to evaluate the bone mineral density, lean mass, frequency of low lean mass and analyze correlation among the activity parameters, duration of the disease, life quality and lean mass indices in women with rheumatoid arthritis.

Materials and methods

461 women aged 40-87 years (age - 57.17 ± 0.71 years) were examined, among them 71 patients with rheumatoid arthritis and 390 controls. We conducted the clinical and laboratory examination. Pain intensity was evaluated by the visual analogue scale, the quality of life – by the HAQ questionnaire. Lean mass, bone mineral density were measured by the X-ray absorptiometry (Prodigy, GEHC Lunar, Madison, WI, USA). Low lean mass was determined when an appendicular lean mass index was less than 5.72 kg/m^2 (V. Povoroznyuk, N. Dzerovych, 2016).

Results

Patients with rheumatoid arthritis had a significantly lower femoral neck mineral density ($p = 0.002$), lean mass of the total body ($p = 0.01$) and appendicular lean mass ($p < 0.01$). We didn't find any significant connection among the activity parameters (C-reactive protein, ESR, pain VAS, DAS-28), duration of the disease, life quality and lean mass indices in patients with rheumatoid arthritis. However, a significant correlation was found between the number of swollen joints and lean mass of upper limbs ($r=0.67$; $p=0.02$). The frequency of low lean mass in women with rheumatoid arthritis was 49 %, in the control group – 18 %.

Conclusions

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Menopause

Bone mineral density in postmenopausal women with osteoarthritis and obesity

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Context
Due to the global aging of the population, the number of chronic diseases has increased noticeably.

Objective
To examine body mass density (BMD) and trabecular bone score (TBS) of postmenopausal women with obesity and OA.

Materials and methods
We have observed 359 postmenopausal women (50-89 years old) and divided them into groups by age decades: 50-59, 60-69, 70-79 and over 80 years old. According to the ACR Clinical classification criteria for knee and hip OA, we have divided them into 2 groups^ group I – 117 females with symptomatic OA (89 patients with knee OA, 28 - with hip OA) and group II –242 women with a normal functional activity of knee and hip joints. Analysis of data was performed taking into account their BMI, classified by World Health Organization (WHO) where obesity was established when BMI was above 30 kg/m^2.

Results
There were observed no differences between age and height across all groups. However, women with OA had a significantly higher BMI and weight compared with group of women without weight problems. Symptomatic OA was detected in 41% of postmenopausal women with obesity (44 women) and normal functional activity of joints - in 58.9% (63 women with obesity).
There were found no significant differences for both groups in BMD of femoral necks (p=0.07 and p=0.33 respectively) and TBS (p=0.06). But, women with symptomatic OA had significantly higher level of lumbar spine BMD compared with woman without OA (p=0.000068).
In the age group 50-59 years OA was detected in 31.8% of women with normal BMI and in 68.2% of those without OA. In the next group - 60-69 years, OA was in 27.2% of women with normal BMI and in 72.8% of those with a normal functional activity of large joints. Amoung 70-79 years old women 25.0% of cases OA with normal BMI vs 75.0% with normal BMI and without OA. In the oldest group of subjects over 80 years, the distribution was 43.8% vs 56.2% with a normal functional activity of large joints. Chi-squared (χ2) test, showed that in postmenopausal women with OA was significantly higher BMI (χ2=5.05, p=0.02).

Conclusion
In the OA patients, the frequency of obesity is significantly higher compared to persons with a normal functional activity of large joints. Women with OA had a significantly higher BMD of lumbar spine. At the same time in our study, there were no significant differences of BMD of femoral necks and TBS.

Menopause

Vitamin D level in Ukrainian postmenopausal women depending on body mass index

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Objective

To detect 25-hydroxyvitamin D level in postmenopausal women depending on BMI.

Materials and methods

There were observed 1007 women, 50-89 years old (the mean age is 65.74±8.61 years old). There were detected 25-hydroxyvitamin D level, weight, height and body mass index (BMI) in all participants. Women were divided into 6 groups according to their BMI: I group – 338 women with normal body weight (NBW) (BMI 18.5-24.9 kg/m^2), II group – 16 women with BMI was less than 18.5 kg/m^2, III group – 382 women with excessive body weight (BMI 25.0-29.9 kg/m^2), IV group – 199 women with obesity class I (BMI 30.0-34.9 kg/m^2), V group – 60 women with obesity class II (BMI 35.0-39.9 kg/m^2) and VI group – 12 women with obesity class III (BMI ≥40 kg/m^2). BMI was calculated by a ratio of body weight (in kilograms) and square of height (in meters), expressed in kg/m^2. Serum level of 25(OH)D was detected by electrochemiluminescent method - Elecsys 2010 analyzer (Roche Diagnostics, Germany) and cobas test system.

Results

Analysis of 25(OH)D level depending on BMI showed revealed the highest level 25(OH)D in women with NBW (28.24±12.99 ng/ml), while the lowest level were in women with obesity of class I (23.60±10.24 ng/ml) and class II (22.38±10.34 ng/ml). According to one-way ANOVA analysis, the BMI has significant influence on 25(OH)D level (F=5.81; p=0.00003).

Women of group 50-59 years with NBW have a higher vitamin D level than patients with obesity of class I (30.75±12.56 vs 26.30±12.29; p=0.04) and class II (30.75±12.56 vs 21.31±6.84; p=0.004). Also, we've detected probable differences in vitamin D level in group of 60-69 (28.47±12.43 vs 23.29±9.80; p=0.001). The highest correlation between the 25(OH)D levels and BMI was observed in women of 50-59 years (r=-0.22; p=0.0002). $\chi 2$ showed a significant difference between normal levels of vitamin D in patients with NBW and obesity of class I ($\chi 2$= 13.9; p=0.002) and obesity of class II ($\chi 2$= 12.2; p=0.005).

Conclusion

In Ukrainian women with obesity were detected significant influence BMI on the vitamin D. Vitamin D deficiency was found in 34.4% of postmenopausal women, insufficiency in 31.4% and normal levels in 34.4%. 25(OH) D levels were significantly lower in women with obesity of class I (23.60±10.24 ng/ml) and obesity of class II (22.38±10.34 ng/ml), compared with women who had NBW (28.24±12.99 ng/ml). Obesity negatively influenced vitamin D level values.

Menopause

Women with natural menopause and surgical menopause: the role of the differences of gamma glutamyl transferase and estrogen

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Objective

In Indonesia 2025 estimated that there'll be 60 million menopausal women and currently only reached 14 million menopausal women or 7.4 percent of the total population but not include women who undergo surgical procedures such as hysterectomy, oophorectomy, the use of chemotherapy, radiotherapy, and other drugs that result in the use of menopause. One of the highest rates of morbidity and mortality due to menopause is cardiovascular disease. There are currently many prospective studies that show an independent role of Gamma glutamyl transferase (GGT) in the pathogenesis and clinical analysis of cardiovascular disease and cardiovascular consequences in general studies. This study aims to analyze the differences in Gamma glutamyl transferase (GGT) and estrogen in women with natural menopause and surgical menopause.

Method

This study is a comparative analytic study with case control design on 67 subject with natural menopause and 67 subject with surgical menopause at Haji Adam Malik Hospital Medan in January to April 2019. Subjects were selected by consecutive sampling and samples obtained from the patient's bloods. Gamma glutamyl transferase and estrogen levels measured by ELISA. Data were analyzed using descriptive statistics and Mann-Whitney test. A p-value <0.05 is applied to each statistical test as significant.

Result

Characteristics of study samples from the natural menopause group were age 55 years, onset of menopause 51 years, menopause length of 5 years, IMT 22.5 kg/m^2, LDL levels 154 mg/dL, HDL levels 49 mg/dL, and TGA 125 mg/dL. While the surgical menopause group in this study found age 54 years, onset of menopause 48 years, menopause length of 6 years, BMI 23.7 kg/m^2, LDL levels 158 mg /dL, HDL levels 52 mg/dL, and TGA 150 mg /dL. BMI of the surgical menopause was found higher than natural menopause (23,7 and 22,5) with p value 0,009. The LDL level of the natural menopause is 154 mg/dL and 158 mg/dL for surgical menopause. Whereas HDL Level of the natural menopause is 49 mg/dL dan 52 mg/dL for surgical menopause with p < 0,001. The Triglycerides (TGA) level didn't differ significantly within both group. The GGT and estrogen were difference and statistically significant between two group with p <0,001.

Conclusion

There was a significant difference in the GGT and estrogen level of the natural menopause women and surgical menopause women.

Keywords: Gamma Glutamyl Transferase, estrogen, natural menopause, surgical menopause

Menopause

Bone mineral density and its association with visceral fat density and follicle stimulating hormone serum levels in post-menopausal patients of the Hospital Juárez de México

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Introduction

Osteoporosis is a disease characterized by low bone mass that impairs the bone tissue microarchitecture, generating bone fragility with higher fracture risk, particularly in hip and spine. Increase in visceral fat is associated with an increase in the synthesis of pro-inflammatory cytokines – which promote bone resorption. On the other hand, the receptors found in the osteoclast for the follicle stimulating hormone favor their differentiation, activity, and survival through various mechanisms.

Objective

Assess the relationship of bone mineral density with the percentage of visceral fat and the follicle stimulating hormone levels in post-menopausal women treated at the Menopause Clinic. Study design: a prospective, cross-sectional and analytical study of cases and Controls was conducted. The post-menopausal patients selected were in stages +1 and +2 of the STRAW + 10 staging system. The following studies were performed in them: measurement of the visceral fat percentage using the Tanita scale, bone densitometry in a clinic of reference certified by the International Clinical Densitometry Society and quantification of the follicle stimulating hormone serum levels. The sample size was calculated taking into account osteoporosis prevalence of 16% for the Mexican population, with a confidence level of 95% and error margin of 7.5%.

Results

148 patients that met the inclusion criteria were recruited. 66 were in the control group and 82 belonged to the study group. The average age of the control group was 51.86 years +/- 5.2, whereas the study group age was 53.8 years +/- 5. A statistically significant inverse relationship was found between the follicle stimulating hormone serum levels and the bone mineral density of the lumbar segment and the femur neck with $p < 0.05$. In terms of the visceral fat percentage, a statistically significant inverse relationship was found of the lumbar segment with $p < 0.05$; however, a statistically significant relationship was not found with the femur neck.

Conclusion

Measurement of the visceral fat percentage and concentrations of the follicle stimulating hormone serum levels can be made at low cost and be assessed in the routine visit of post-menopausal women to identify those at higher risk of presenting lower bone mineral density, major osteoporotic fracture and hip fracture, with the purpose of providing an early diagnosis and treatment of osteopenia and osteoporosis.

Menopause

Replenish trial: endometrial protection with a 17ß-estradiol and progesterone combination (TX-001HR) in postmenopausal women with vasomotor symptoms

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Introduction

TX-001HR (approved as Bijuva® in the US, TherapeuticsMD, Inc., Boca Raton, FL) is a hormone therapy (HT) of combined naturally occurring 17β-estradiol and progesterone (which some call bio-identical) in a single, oral softgel capsule developed to treat menopause-related vasomotor symptoms (VMS). More than 3M women are estimated to use unapproved compounded bio-identical HT (BHT) in the US, and it is also used outside of the US. Compounded BHT may be associated with endometrial cancer.

Objective

To determine the endometrial safety of four doses of TX-001HR vs placebo in women seeking relief for VMS.

Methods

REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR in postmenopausal women (N=1835; 40–65 years) with an intact uterus and vasomotor symptoms. Women received daily TX-001HR estradiol/progesterone: 1.0 mg/100 mg (n=415), 0.5 mg/100 mg (n=424), 0.5 mg/50 mg (n=421), 0.25 mg/50 mg (n=424) or placebo (n=151). The primary safety endpoint was the 12-month incidence of endometrial hyperplasia based on a consensus read of 2 out of 3 pathologists. Adverse events (AEs) were also monitored.

Results

The incidence of endometrial hyperplasia or malignancy was 0% (by consensus read) with all four TX-001HR doses and placebo after 12 months of therapy. A high incidence of amenorrhea was achieved with all TX-001HR doses.

Conclusions

TX-001HR had a safe endometrial profile in postmenopausal women seeking relief for VMS. No endometrial hyperplasia or malignancy, or unexpected safety issues were observed, which is in contrast to what has been reported with compounded BHT. If approved, TX-001HR may be an alternative option of naturally occurring estradiol and progesterone that can be used to treat hot flushes for the estimated millions of postmenopausal women currently using unregulated, unapproved, compounded BHT, whose efficacy and safety have not been studied in rigorous clinical trials.

Menopause

Replenish trial: TX-001HR (17ß-estradiol and progesterone combination) significantly improved moderate to severe hot flushes in postmenopausal women

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Introduction

TX-001HR (approved as Bijuva® in the US, TherapeuticsMD, Inc., Boca Raton, FL) is a hormone therapy (HT) of naturally occurring 17β-estradiol combined with progesterone (which some call bio-identical) in a single, oral softgel capsule developed to treat menopausal vasomotor symptoms (VMS). No similar combination HT product has been approved yet in the US or Europe.

Objective

To determine efficacy of four TX-001HR doses vs placebo in women with moderate-to-severe hot flushes.

Methods

REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial evaluating TX-001HR in postmenopausal women (N=1835; 40–65 years) with an intact uterus. The VMS substudy included women with moderate to severe hot flushes (≥ 7 hot flushes/day or ≥ 50/week) were randomized to daily TX-001HR estradiol/progesterone 1.0 mg/100 mg (n=141), 0.5 mg/100 mg (n=149), 0.5 mg/50 mg (n=147), 0.25 mg/50 mg (n=154) or placebo (n=135). Four co-primary efficacy endpoints were change from baseline in the frequency and severity of hot flushes at weeks 4 and 12 vs placebo.

Results

TX-001HR 1.0 mg/100 mg or 0.5 mg/100 mg met all 4 co-primary endpoints, with significant improvements from baseline in frequency and severity of moderate to severe hot flushes at weeks 4 (all, $P< 0.05$) and 12 (all, $P< 0.001$) compared with placebo. Women treated with TX-001HR 0.5 mg/50 mg had significant improvements in hot flush frequency and severity at week 12 (both, $P< 0.05$) vs placebo, while those taking 0.25 mg/50 mg had significant improvements in frequency, but not in severity, at weeks 4 and 12 (both, $P\leq 0.001$).

Conclusions

TX-001HR 1.0 mg/100 mg or 0.5 mg/100 mg effectively treated menopause-related moderate to severe hot flushes. If approved, TX-001HR - the first combination HT product containing naturally occurring 17β-estradiol and progesterone - may provide an alternative option for the estimated millions of women currently using unregulated, unapproved, compounded bio-identical HT.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Non-tamoxifen cystic atrophy in postmenopausal women: correlation between hysteroscopic appearance of cystic protuberance, serum estradiol levels and histopathological diagnosis

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Objective
The aim of the study is to correlate between hysteroscopic appearance of cystic protuberance, serum estradiol levels and histopathological (HPE) results of endometrial biopsies in the assessment of non tamoxifen post menopausal bleeding

Methods
This is a hospital based study prospective observational study. 66 women reported with postmenopausal bleeding. Out of them, 20 women had hysteroscopic appearance of cystic protuberance of the endometrium w analysed. All of them presented with minimal vaginal bleeding. Transvaginal ultrasound was done with voluson GE-S 10 expert. Outpatient hysteroscopy with endometrial biopsy was sent for histopathological assessment. Hysteroscopy was performed without anaesthesia using a 5 mm continuous flow Bettocchi Office Hysteroscope, Karl Storz with biopsy and grasping forceps. Normal saline was used as distention media and pressures were controlled by hamou endomat. Blood serum estradiol levels were analysed using chemiluminescence immunoassay method.

Patients
20 post menopausal women

Intervention
20 women with postmenopausal bleeding were subjected to hysteroscopic guided endometrial biopsy, and the results were compared with serum estradiol levels and histopathological results of endometrial biopsies from January 2018 to November 2019.

Main outcome measure
Correlation between hysteroscopic appearance of cystic protuberance with serum estradiol levels of < 37 pg/ml (biological reference, age /gender specific) and histopathological results of endometrial tissue biopsy.

Results
Amongst the 20 women with hysteroscopic diagnosis of cystic protuberance, 18 had serum estradiol levels of < 37 pg/ml. 1 of them aged 71, with HPE of senile cystic atrophy had a serum estradiol levels of 75 pg/ml. Her body mass index(BMI) was 35 and there were no other associated risk factors for endometrial cancer. S. Estradiol levels of 60 pg/ml was observed in a woman aged 63 years, the HPE showed adenoleiomatous polyp on the background of atrophic endometrium. She has a BMI of 33, and is a known diabetic and hypertensive. None of the women in this analysis were on menopausal hormone therapy nor on tamoxifen.
Histopathology results of the 20 women were reported as follows-17 showed senile cystic atrophy, 2 had atrophic endometrium. One woman age 55, BMI 24, menopause 2.5 years ago, known hypertensive since 5yrs showed disordered proliferative endometrium. Her serum estradiol level was 18 pg/ml.
In these series of cases, the associated pathology seen were endometrial polyp (7) and FIGO type 0 myomas (2).

Conclusions
Cystic protuberance on hysteroscopy is a benign condition, and is not related to endometrial hyperplasia and hence not at an increased risk for endometrial adenocarcinoma. Cystic protuberance may be associated with other pathologies. Serum estradiol levels seem to correlate well with hysteroscopic and histopathological results.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Anti-müllerian hormone as a useful marker for the management of polycystic ovary syndrome

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Context

Excessive ovarian production of Anti-Müllerian Hormone (AMH) is now considered as an important feature of PCOS.

Objective

Determine the possibility of using AMH for the diagnosis of PCOS, and evaluate the efficacy of different treatment methods by assessing serum AMH levels.

Methods-Patients

220 women (14-30 years) were involved in the prospective study. 160 patients with PCOS and 60 controls. The diagnosis of PCOS was based on the criteria of Rotterdam Consensus 2003. All patients underwent hormonal and ultrasound investigation on day 2-3 of menstrual cycle before and after the treatment (AMH, luteinizing hormone (LH), total testosterone (T), free testosterone (FT), volume of the ovaries (Ov/v), the number of antral follicles (AFC)). Body mass index (BMI), homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated. Hirsutism was evaluated on the Ferriman-Gallwey modified scale (mFG).

PCOS patients was divided into two: Group I –without insulin resistance (n=70); Group II – with insulin resistance (n=90). Group I was treated with OCs (drospirenone 3 mg/ethinylestradiol 30 μg). Group II was divided into treatment subgroups of 30 patients each: Subgroup A received OCs; Subgroup B – myo-inositol (2 g twice a day); subgroup C – OCs + myo-inositol. Data was analyzed at baseline, 3 and 6 months of treatment.

Results

Average AMH level in PCOS patients were significantly higher compared to controls ($p<0.001$).

In Group I and Group II, subgroup A the average level of AMH, LH, FT, T, Ov/v, AFC and FG significantly decreased ($p<0.001$) after administration of OCs, but HOMA-IR, BMI did not change significantly.

In Group II subgroup B-HOMA-IR and BMI significantly decreased ($p<0.001$) after the treatment with myo-inositol; other parameters did not change significantly.

In Group II subgroup C- AMH, LH, FT, T, Ov/v, AFC, HOMA-IR, BMI and mFG significantly decreased ($p<0.001$) after administration of OCs+ myo-inositol.

Conclusion

AMH may be considered as a diagnostic marker of PCOS.

Treatment with OCs significantly decreases level of AMH, Ov/v, AFC, clinical and biochemical hyperandrogenism in PCOS patients.

A combined treatment with myo-inositol and OCs may be more effective in controlling endocrine and metabolic profiles in PCOS patients with insulin resistance, than usage of OCs alone.

AMH is considered as useful marker for the assessment of the treatment efficacy in PCOS patients.

I have no financial relationships to disclose.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Correlation between hysteroscopic findings and pathological anatomy for the diagnosis of endometrial polyps in patients with abnormal uterine bleeding

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Introduction
Endometrial polyps are benign nodular protrusions of the endometrial surface. Its prevalence is high, especially in patients with abnormal uterine bleeding and it is associated with infertility and endometrial cancer. The gold standard for its directed study and management is hysteroscopic resection.

Objective
To determine the correlation between hysteroscopic findings and pathological anatomy in patients with abnormal uterine bleeding intervened at Concepcion Clinical Hospital, Chile, between 2016 and 2017.

Method
Descriptive cross-sectional study. A sample of 240 patients abnormal uterine bleeding, with or without suspicion of endometrial polyp whose ages fluctuate between 20 and 78 years, who underwent hysteroscopy and directed biopsy at gynecology unit between 2016 and 2017, is analyzed. Univariate analysis was performed for qualitative and quantitative variables. The analyzes were performed with Stata V.14, with a significance level of 0.05.

Results
The average age was 49 years. 55% of patients had ultrasound suspicion of endometrial polyp at the time of the intervention, 29% thickened endometrium, 5% uterine fibroid and 11% other diagnoses. Of the total of patients, 59% had a lesion compatible with endometrial polyp to hysteroscopy, 50% positive biopsy for endometrial polyp, and in 44% there was a correlation between hysteroscopic finding and pathological anatomy. The prevalence of endometrial polyp in the sample studied was 50%. The agreement between hysteroscopic finding and pathological anatomy for endometrial polyp had a sensitivity of 87.4% and specificity of 70.0%, and a positive predictive value of 74.3% and negative predictive value of 84.8%. The LR (+) and (-) were 2.91 and 0.18 respectively.

Conclusion
There is high agreement between visualization of a lesion compatible with endometrial polyp to hysteroscopy and the pathological finding, this study is essential to rule out malignancy or other non-evident premalignant lesions in direct vision by hysteroscopy in patients with abnormal uterine bleeding.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

The role of epigenetic changes in endometrial polyp's pathogenesis and recurrence

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National Medical Research Center of Obstetrics, Gynecology, and Perinatology named after Academician V.I. Kulakov of the Ministry of Health of the Russian Federation

Context

Endometrial polyps (EP) can be considered the most common intrauterine pathology, characterized by abnormal uterine bleeding (AUB) and a high recurrence rate. The pathogenesis of EP is not yet fully understood. EP's formation is assumed to be associated with excessive proliferation and angiogenesis, which may be enhanced by activation of Wnt-signaling pathway. This may be related to epigenetic silencing of the suppressor genes, in particular, with Wnt inhibitory factor 1 (WIF1) hypermethylation, which was detected in endometrial cancer (EC). However, its role in EP has not been studied yet.

Objective

To determine the role of WIF1 gene methylation in in EP's pathogenesis and recurrence.

Subjects and methods

The study involved 130 women of reproductive age with histologically confirmed EP and 20 women with normal endometrium. All patients with EP were followed up for 12 months with ultrasound examination to detect the recurrence onset. Bisulfite sequencing method was used to evaluate the methylation status (methylation frequency and the number of methylated sites) of WIF1 gene in 60 EP samples and 20 samples of normal endometrium.

Results

In EP, WIF1 gene methylation was detected in 61.7%, while in the control group – in none of cases. In EP, the number of methylated sites ranged from 1 to 13. The EP recurrence rate over 12 months equaled to 17.1%. It was revealed that WIF1 gene methylation was found in 85.7% of recurrent EP and in the group without relapses – only in 33.3% of cases. So, therefore, methylation detection increased the recurrence probability by 4.67 times (RR = 4.67; 95% CI [1.24; 17.54]; p <0.001). The presence of methylation did not depend on endometrium morphology, clinical and anamnestic data.

Conclusion

EP formation and recurrence can be based on epigenetic disorders of the WIF1 gene, which leads to activation of the Wnt-pathway, cell proliferation, and angiogenesis. We suggest, that evaluation of EP's methylation status could predict the probability of recurrence, however, the causes of hypermethylation in EP's are still to be established.

Key words

Endometrial polyp, epigenetics, methylation, Wnt-pathway, WIF1, recurrence.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

The risk of developing uterine fibroids in women of reproductive age with polymorphism of insulin-like growth factors II

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Myoma of the uterus is one of the most common tumors of the reproductive system and is found in 20-25% of women over the age of 30. Uterine fibroids is one of the main causes of abnormal uterine bleeding, iron deficiency anemia, urinary disorders, pelvic pain, dyspareunia, reduced fertility, miscarriage, which significantly affects the quality of women life.

Objective

Study the genetic polymorphism of 3123 G/A insulin-like growth factor II in women with uterine myoma.

Materials and methods

82 patients were examined. The main group consisted of 42 women who underwent surgical intervention and histologically verified the diagnosis of uterine fibroids. Control group - 40 patients undergoing routine medical examination. All examined had a fence of venous blood in the morning on an empty stomach. Isolation of genomic DNA was performed from venous blood by a standard phenol-chloroform extraction method. Genotyping of polymorphism of IGF-II genes was carried out by means of a multiplex polymerase chain reaction according to the protocol of G.V. Dedoussis et al.

Results

Statistically significant differences were obtained when comparing allele frequencies between patients of the main and control groups: the allele G frequency in the main group was 0,638, and the allele A was 0,193 ($p<0,05$); In the control group, the allele frequency G is 0,596, and the allele A is 0,275 ($p<0,05$). The following regularities were found in the genotype distribution of polymorphism of the IGF II 3123 G/A gene: the homozygous mutant AA genotype is statistically significantly more frequent in the control group ($p<0,05$) than in the main group. Carrying of variant genotypes 3123 G/A IGF II is associated with the development of uterine fibroids. It was found that the frequencies of alleles and frequencies of genotypes in the main and control groups differ significantly in polymorphism 3123 G/A IGF II. It should be noted that polymorphic variant G/G 3123 G/A IGF II may be associated with an increased risk of uterine fibroids.

Conclusions

The obtained results on the protective A-allele 3123 G/A polymorphic variant IGF II, can be used to calculate the individual risk of uterine fibroids in women with a hereditary and gynecological anamnesis.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Androgenemia is negatively associated with prevalence of uterine fibroids: the results of population-based cross-sectional study

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Objective

To determine the influence of androgens on the prevalence of uterine fibroids in an unselected population of reproductive-age women.

Methods

1481 women of reproductive age were recruited during the institution-based, cross-sectional study in 2016-2019. All women wrote informed consent. The exclusion criteria were as follows: a) current pregnancy or lactation; b) history of hysterectomy, bilateral oophorectomy, endometrial ablation, and or uterine artery embolization. All women underwent a standard medical examination and pelvic ultrasound. Serum samples of all women were analyzed for total testosterone (TT) using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS), and DHEAS and sex hormone binding globulin (SHBG), prolactin, by ELISA. The Free Androgen Index (FAI) was calculated (i.e. [TT/SHBG] x 100). Data is presented as Mean (Std). The study was approved by the local ethics committee.

Results

Of 1481 examined women uterine fibroids were found in 199 subjects (13,4%), who had significantly lower values of testosterone compared to women without uterine fibroids – 26.8 (23.0) ng/dl vs 33.5 (33.8) ng/dl (p=0.007), accordingly. DHEAS levels were higher in the group of women without fibroids: 181 (92) vs 152 (71) pg/ml in women who had uterine fibroids (p=0.0001). There was no significant difference between calculated FAI in women with and without uterine fibroids. It was also shown that BMI was higher in women with fibroids: 27,3 (5.8) vs 25,3 (5.4) kg/m^2 (p=0.0001).

Conclusions

Based on the results of our study we can conclude that androgens levels are negatively associated with the prevalence of uterine fibroids and seem to be a “protective” factor.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Metformin use is associated with a lower risk of uterine leiomyoma in female type 2 diabetes patients in Taiwan

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Background
Whether metformin may reduce the risk of uterine leiomyoma in type 2 diabetes patients has not been investigated. This retrospective cohort study compared the risk of uterine leiomyoma in ever versus never users of metformin.

Methods
Female patients with new-onset type 2 diabetes during 1999-2005 were enrolled from the reimbursement database of Taiwan's National Health Insurance and followed up from January 1, 2006 until December 31, 2011. Analyses were conducted in a propensity score (PS) matched-pair cohort of 10998 ever users and 10998 never users of metformin. Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using the PS.

Results
A total of 321 never users and 162 ever users developed uterine leiomyoma during follow-up, with respective incidence of 704.65 and 329.82 per 100000 person-years. The overall hazard ratio was 0.467 (95% confidence interval: 0.387-0.564). The hazard ratios for the first (<23.3 months), second (23.3-53.1 months) and third (>53.1 months) tertiles of cumulative duration were 0.881 (0.685-1.132), 0.485 (0.367-0.642) and 0.198 (0.134-0.291), respectively; and were 0.751 (0.576-0.980), 0.477 (0.360-0.632) and 0.277 (0.198-0.386), respectively, for the first (<655000 mg), second 655000-1725500 mg) and third (>1725500) tertiles of cumulative dose. Sensitivity analyses after excluding users of sulfonylurea, users of estrogen, users of insulin, users of incretin-based therapies during follow-up, patients with irregular drug refills, patients who discontinued the use of metformin, patients who received metformin prescription <4 times or redefining uterine leiomyoma by using "diagnostic code" plus "procedure codes" consistently supported a lower risk of uterine leiomyoma in ever users of metformin.

Conclusion
Metformin use is associated with a lower risk of uterine leiomyoma.

Gynecology: angiogenesis, AUB, pelvic pain, endometrial hyperplasia, myoma and adnexal cysts

Impact of glypressin in laparoscopic myomectomy

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Introduction

The most common benign tumor of the female genital tract is myoma. Hysterectomy is the definitive treatment; but myomectomy remains the gold-standard treatment for women who want to preserve their fertility. A major myomectomy-associated problem is excessive blood loss. Pharmacological interventions have been introduced to reduce hemorrhage during myomectomy.

Aim

To evaluate the effect of glypressin on blood loss during laparoscopic myomectomy (LM) in women with uterine myomas.

Material and method

One hundred eighty-eight women scheduled for LM for uterine myomas were divided into two groups. Sixty-four women received intramyometrial injection of glypressin 0,2 mg/ml - 5 ml (glypressin group). One hundred twenty-four cases had a LM performed without any other method to reduce blood loss. The decrease in postoperative hemoglobin (Hb), hematocrit (Ht), morbidity and duration of hospital stay were assessed.

Results

Hb and Ht (as it were presumably) followed similar changes in our study. We find changes that were statistically proved ($p<0.05$) between groups, for the Hb and Ht decrease, after LM Hb after LM.

Discussions and conclusions

The impact of glypressin administration in hemorrhage control in uterine leiomyomas may establish new future perspectives, regarding its administration in gynaecological hemorrhagic pathologies.

Female sexual function and dysfunction

Clinical trial with topical use of estrogen, testosterone and vaginal dilator in women with cervical cancer after radiotherapy – evaluation of sexual function

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Context
Pelvic radiotherapy is associated with late adverse events. Among them, vaginal stenosis is the most frequent. Few studies have evaluated the effects of different treatments for vaginal stenosis on aspects related to sexual function after radiotherapy.

Objectives
To evaluate the effects of different therapeutic modalities for vaginal stenosis on the sexual function of women with cervical cancer after pelvic radiotherapy.

Methods
Clinical trial of 195 women referred for radiotherapy, randomized to receive topical estrogen (66), topical testosterone (34), vaginal dilator (29) or lubricating gel (66) for one year, starting soon after the end of radiotherapy from 01/2013 to 05/2018. The outcome variable was sexual function assessed through the Female Sexual Function Index (FSFI) questionnaire. Evaluations were performed shortly after radiotherapy, 4 months, 8 months and one year after treatment. Statistical analysis was carried out using chi-square test, Kruskal-Wallis test and ANOVA for repeated measures.

Results
The mean age of women was 46.78 (±13.01) years, 61.03% were premenopausal and 73.84% had stage IIB-IIIB tumors. Before the beginning of the intervention, 33.8% of the total group of women reported sexual activity. Among them, 63.6% had sexual dysfunction (FSFI <26.5). During the 12 months of follow-up, women who were sexually inactive reported episodes of sexual intercourse. At 12 months, 56.3% reported sexual activity, and 63.7% reported dysfunction (FSFI <26.5). There was no significant difference in the frequency of sexual dysfunction (FSFI <26.5) between the studied groups at any of the evaluated moments. By comparing scores from the different FSFI domains between study groups and assessment times (interaction groups versus times) only among sexually active women who completed all assessments during the 12 months of intervention, we observed that the estrogen group showed significant improvement in the desire domain ($p < 0.01$) compared to all other groups and in the pain domain ($p = 0.03$) compared to the dilator group.

Conclusions
The prevalence of women with cervical cancer who have undergone pelvic radiotherapy that maintains sexual activity increases over time after the end of treatment. Vaginal topical estrogen may decrease pain during intercourse and lead to increased sexual desire in these women.

Female sexual function and dysfunction

Evaluation of the effect of prasterone (DHEA) in the treatment of hypoactive sexual desire and its impact on different metabolic and anthropometric parameters in postmenopausal women; one year follow-up

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Context

Menopause is a stage associated with a deficit in the production of estrogens and androgens in women. These endocrine changes have an adverse impact on their health. DHEA is a precursor of androgens and estrogens, which during menopause are reduced by up to 60% and represents almost the only exclusive source of sex steroids at this stage. Its oral administration has been shown to improve body composition and various metabolic variables. Efficacy regarding sexual function is controversial. This is the first study in Mexico to evaluate these variables with DHEA produced in our country.

Objective

To determine the effect on sexual function (FS), somatometry, BMD and metabolic variables with the administration of 50 mg DHEA (BIOLAIF 50 mg, Medix, México) orally for 12 months in menopausal patients.

Methods

Prospective-Clinical Study. Statistical analysis: Descriptive statistics by two dimensional analysis of Friedman, version 22 spss.

Patients

A sample calculation was made based on the formula of an infinite population of 29 postmenopausal patients.

Interventions

Clinical assessment, monthly follow-up, laboratory and cabinet studies.

Main outcome measure

FS index, BMD of full body, weight, height, body mass index (BMI), muscle mass (MM), fat mass (FM), appendiceal muscle mass (MMA), lipid profile, glucose, insulin, HOMA (assessment of the homeostatic model) and serum DHEA.

Results

Average age 53.03 years, average of the age of beginning of her menopause 48.3 years. The sexual function index average evaluated at six months in 29 patients increased from 10.8 to 28.1 and at 12 months, in 18 patients from an average of 10.6 to 29.1. In relation to the metabolic evaluation the dimensional analysis of Friedman for total cholesterol, LDL cholesterol, triglycerides, glucose, insulin and HOMA Index at 0,3,6 and 12 months were no significant ($p \geq 0.05$), HDL cholesterol measured al 0,3,6 and 12 months discretely increased with a $p=0.00$, in regards to body composition, the fat mass, body weight, BMI measured at 0,3,9 and 12 months there was no statistical difference ($p \geq 0.05$), the muscular mass measured basal and at 12 months was no significant with a $p \geq 0.05$, however regarding bone mineral density there was a slight increase with a $p \leq 0.05$. Conclusion. The daily administration of 50 mg of DHEA orally for 12 months significantly improved the IFSF, without affecting the metabolic profile, the body composition and kepping bone mineral density and muscular mass.

Female sexual function and dysfunction

Does complete weight restoration and menstrual recovery improves sexual function of female adolescents with Anorexia Nervosa?

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Context-Objective

The aim of this study is to assess the role of complete weight restoration and menstrual recovery in sexual dysfunction of adolescents diagnosed with Anorexia Nervosa (AN).

Methods-Patient(s)-Intervention(s)

Prospective study of 60 adolescents presented with secondary amenorrhea and diagnosed with AN based on DSM-IV criteria. Anthropometrics, body composition by dual-energy X-ray absorptiometry (DXA), hormonal studies, responses to mental health screens (EAT-26) and Structured Interview for Anorexic and Bulimic Disorders–psychopathology scale (SIABP) concerning intimacy, libido, sexual anxiety, partner and sexual relationships were obtained at the beginning and at complete weight restoration, in all adolescents, independently of menstrual recovery (Group A) or not (Group B)

Main outcome measure(s) and result(s)

At first attendance Girls of Group A had no statistically significant differences ($p>0.05$) with these of Group B regarding loss of libido, sexual anxiety and partner relationships (avoidance or absence). After complete weight restoration, loss of libido, sexual anxiety and partner relationships (avoidance or absence) reported in statistically significantly lower ($p<0.01$) degree in adolescents of Group A compared to these of Group B. Sexual anxiety and loss of libido were negatively correlated with total body fat mass (%) ($r=-0.456$, $p<0.01$) ($r=-0.567$, $p<0.01$) respectively and trunk fat mass (%) ($r=-0.512$, $p<0.01$) ($r=-0.644$, $p<0.001$) respectively in girls of Group A, after complete weight restoration and menstrual recovery.

Conclusions

Sexual dysfunction is common across adolescents with AN. Complete weight restoration and menstrual recovery improves loss of libido, sexual anxiety and partner relationships in these girls, while sexual anxiety and loss of libido is negatively correlated with total body fat mass (%) and trunk fat mass (%).

Female sexual function and dysfunction

Menopausal symptoms and quality of life according to the presence of alterations in genital lubrication. Study in climacteric Afrodescendant women

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Context
Estrogenic reduction in climacteric produces urogenital changes: loss of elasticity, shortening and vaginal tightness, which are expressed among other forms, with alterations of genital lubrication (AGL). There is not enough quality of life (QoL) assessment in afrodescendant climacteric women.

Objective
To compare menopausal symptoms and QoL in afrodescendant women according to the presence of AGL

Methods
Cross sectional study of CAVIMEC (quality of life in menopause and Colombian ethnic groups) project. Anonymous and voluntary participation, approved by the ethics committee, University of Cartagena, Colombia. Two groups were formed: with AGL (score<3 in the third question of Female Sexual Function Index-6) and without AGL (score>3). Quantitative variables are presented in $\dot{X}$±SD and qualitative variables in %. The significance of the differences between groups was established according to homogeneity of the variance. Logistic regression was performed with AGL (independent variable) and Menopause Rating Scale (MRS) domains (dependent variable). Menopausal symptoms were correlated with genital lubrication

Patients
Afrodescendant women from the Colombian Caribbean. 40-59 years old, healthy, captured by interviewers in their residences.

Intervention
Sociodemographic characteristics form, Menopause Rating Scale and the Female Sexual Function Index (FSFI-6).
Measurement of the primary outcome: menopausal symptoms and QoL

Results
369 women were studied. 33(8.9%) with AGL and 336 (91.1%) without AGL. Age 49.6±5.3, older those with AGL (p<0.01). Postmenopausal 45.5%. Scholarship 8.6±4.2; BMI 27.4±4.6; waist/hip ratio 0.86±0.09; daily cups of coffee 1.6±1.6; smokers 13.8%, hormone therapy 12.2%; arterial hypertension 12.2% and diabetes 23.0%, without differences according to AGL (p>0.05). Women with AGL had more sexual and urinary problems, depressed mood, irritability or anxiety (p<0.05). No differences were observed in hot flashes and sleep disturbance. AGL was associated with severe psychological deterioration OR: 2.74 [95%CI:1.10-6.85]p=0.03, urogenital OR:4.34 [95%CI:2.08-9.05]p<0.001 and QoL OR: 2.66[95%CI:1.22-5.82]p=0.01. Significant negative correlation between genital lubrication and sexual problems rho:-0.38 [95%CI:- 0.43to-0.34]; urinary rho:-0.46 [95%CI:-0.514to-0.408] and QoL rho:-0.080 [95%CI:- 0.086to-0.074]

Conclusion
Afrodescendant climacteric women with AGL had more urogenital and psychological symptoms and worse QoL than AGL- free women.

Female sexual function and dysfunction

Sexual function in Afrodescendant climaterics with severe urogenital symptoms. Assesment with short female sexual function index

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Context
Sexuality is an important part of women's wellbeing and an indicator of quality of life. WHO has declared 2015-2024 period as a decade of afro-descendants to foster attention of these ethnic communities, in them are few studies that assess sexual function according to presence of urogenital symptoms.

Objective
Estimate prevalence of sexual dysfunction (SD) in afro-descendants according to presence of severe urogenital symptoms (SUGS).

Methods
Cross-sectional study, part of project CAVIMEC (Quality of life in Menopause and Colombian Ethnic Groups). Anonymous and voluntary participation, approved by ethics committee, University of Cartagena, Colombia.
Two groups were formed: with SUGS (score >3 in urogenital domain of MRS, usually defined severe urogenital impairment) and without SUGS (score <3).
Data are expressed as Ẋ±SD for continuous data, and percentages for categorical data. Significance of differences between groups was established according to homogeneity of variance. Logistic regression was performed with SD (dependent variable) and SUGS (independent variable).

Patient (s)
Women living in populations of western Colombia, which are afro-descendant settlements. Age 40-59 years, healthy, identified in their residences, with black skin, self-recognized as Afro-descendants and daughters of father and mother of equal ethnic condition. Pregnant women and those with cognitive disabilities were excluded.

Intervention (s)
A form of sociodemographic characteristics, Menopause Rating Scale (MRS) and short Female Sexual Function Index (FSFI-6) were applied.

Main outcome measure (s)
SUGS and SD, as well as different types of SD.

Outcomes
Study in 372 women who had sexual partner and had had intercourse in the last four weeks. 270 (73,4%) without SUGS and 99 (26,6%) with SUGS. No differences between groups in: diabetes, nutritional status, central obesity and coffee consumption. Women with SUGS were older, 54,2±4,3 vs 48,0±4,6, p<0,01. There was greater alteration of desire, excitement, lubrication, orgasm, satisfaction and more presence of pain, in those with SSUG (p <0,01). They also had more SD: 73,7% [95%CI:63,9-82,1] compared to 15,1% [95%CI:11,1-20,0] in women without SUGS, p<0,01.
SUGS was associated with SD OR:3,2[95%CI:1,7-6,2] p<0,01 Conclusion. Significant statistical association was observed between SD and SUGS.

Female sexual function and dysfunction

Sex steroids make little contribution to sexual function in reproductive-aged women

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Context
Whether serum androgens are determinants of sexual function in reproductive-aged women remains uncertain.

Objective
To determine the associations between androgens and sexual function in premenopausal women

Methods
The Grollo-Ruzzene Younger Women's Health Study (GR Study) was a cross-sectional study of 6896 community-based women, aged 18-39 years, recruited from the eastern Australian states, between November 2016 and July 2017. This analysis included participants who provided a blood sample, had regular menstrual cycles, were not pregnant, breast-feeding or using systemic steroids.

Patient(s)
N/A

Intervention(s)
N/A

Main outcome measure(s)
Sexual function was assessed using the Profile of Female Sexual Function and sex steroids were measured by liquid chromatography-tandem mass spectrometry

Result(s)
588 women provided complete data. Adjusting for age, body mass index, cycle stage, smoking, parity, partner status and psychoactive medication, sexual desire was positively associated with serum DHEA and androstenedione (β-coefficient 0.58, 95% CI 0.06-1.10, p=0.03 and 1.98, 95% CI 0.05-3.92, p=0.05, respectively), and negatively with SHBG (β-coefficient -0.09, 95%CI -0.15-0.03, p=0.003). Each model explained <4% of the variation in sexual desire. Responsiveness was associated with androstenedione (p=0.03); non-normality of this data precluded adjustment for potential confounders. There were no statistically significant associations between serum testosterone, 11-ketoandrostenedione or 11-ketotestosterone and any sexual domain, or between arousal or orgasm and any hormone.

Conclusions
Although pre-androgen levels are modestly associated with sexual desire in premenopausal women, their measurement is not diagnostically useful. The inverse association between sexual desire and SHBG highlights the need for greater understanding of this enigmatic glycoprotein.

Female sexual function and dysfunction

The prevalence of sexual difficulties in young Australian women aged 16-44

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Monash University

Context
There are little data pertaining to sexual function of premenopausal women. The available data are limited by the use of convenience samples or questionnaires that rely on women having a heterosexual partner and engaging in penetrative sex, or being sexually active.

Objective
To document the prevalence of female sexual dysfunctions (FSDs) and factors associated with FSDs and sexually-related personal distress in premenopausal women.

Methods
Cross-sectional online survey

Patient(s)
Representative sample of 6,986 community-based women aged 18-39 years from the Eastern states of Australia

Intervention(s)
N/A

Main outcome measure(s)
Women were classified as having sexually-related personal distress if they had a Female Sexual Distress Scale-Revised score of >11, and as having an FSD if they had a low Profile of Female Sexual Function desire, arousal, orgasmic function, responsiveness or sexual self-image domain score plus sexually-related personal distress. Socio-demographic factors associated with an FSD were examined by multivariable logistic regression.

Result(s)
The prevalence of sexually-related personal distress was 50.2% (95% confidence interval 49.0-51.4). Sexually-related personal distress without dysfunction affected 29.6%, whereas 20.6% had at least one FSD. The proportions of women with self-image, arousal, desire, orgasm and responsiveness dysfunction were 11.1%, 9%, 8%, 7.9% and 3.4% respectively. Sexual self-image dysfunction was associated with being overweight ($p<0.001$), obese ($p<0.001$), in a de facto relationship ($p<0.001$), married ($p=0.05$), breastfeeding ($p=0.001$) and taking a psychotropic medication ($p<0.001$). Psychotropic medication was significantly associated with all FSDs ($p<0.001$). Independent risk factors for non-specific sexually-related personal distress included psychotropic medication ($p<0.001$), sexual inactivity ($p<0.001$) and infertility treatment ($p<0.001$).

Conclusions
That half of young Australian women have sexually-related personal distress and one in five women have at least an FSD, with sexual self-image predominating, is concerning. The high prevalence of distress signals the importance of health professionals being adequately prepared to discuss sexual health concerns.

Female sexual function and dysfunction

The effect of cigarette smoke on female reproductive system: a mouse model

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Context

Increasing evidences demonstrate the noxious effects of cigarette smoke on ovaries with regard for the processes of folliculogenesis, steroidogenesis and gametogenesis. In addition, the harmful impact of cigarette smoke on uterus and on the process of embryos implantation is suggested by the cumulative data showing the negative impact of smoking on natural conceiving and *in vitro* fertilization (IVF) cycle outcome.

Objective

Our study aims to understand the effects of cigarette smoke exposure on miRNAs pattern in mouse oocytes using an *in vivo* model of whole body exposure.

Methods

C57BL/6 mice were whole-body exposed to three cigarettes daily, 7 days/ week, for 2 or 4 months by a specific rodent ventilator. The used regimen of exposure was developed based on information from other studies investigating the toxicological effects of cigarette smoke on ovaries. Mice were superovulated and oocytes collected. MII oocytes pools obtained by single animals were deprived of cumulus cells and used to analyze the miRNAs expression profile.

Results

The global miRNAs changes in mouse oocyte in response to cigarette smoke exposure were disclosed. Our results revealed a significant modulation of miRNAs mainly involved in inflammatory processes, cellular proliferation, and apoptosis. Smoke exposure induced an early downregulation of Dicer1. More to the point, miRNAs expression was altered in a time-dependent manner. Transcriptional alterations of the modulated miRNAs major targets, estrogen receptor 1, peroxisome proliferator-activated receptor-alpha, and tumor protein 53, as well as that of other key regulatory genes, were evidenced.

Conclusions

It is the the first study to disclose the effect of smoke exposure on the ovulated MII oocyte epigenetic system. This study open new roads toward the identification of biomarkers of oocyte toxicity cigarette smoke-induced and knowledge from combined data on individual miRNAs, families of miRNAs and matched mRNA target data will provide to a more comprehensive view of biological systems and their regulation over time.The effect of cigarette smoke on female reproductive system: a mouse model.

Female sexual function and dysfunction

A prospective randomized clinical trial for evaluating the vaginal application of a HYDEAL-D based gel in promoting the restoration of sexual function in the postpartum period: a preliminary analysis

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Context

During postpartum, the vaginal epithelium tends to have an impaired degree of hydration and lubrication due to estrogens and progesterone levels drop. This may lead to vaginal dryness, burning sensation, dyspareunia, or itching, which negatively affect the sexual function of puerperal women.

Objective

This study aimed to evaluate the efficacy of prolonged-release hyaluronic acid derivative vaginal gel on promoting the restoration of sexual function in the postpartum period.

Methods

This is a preliminary analysis on 48 patients enrolled in a prospective randomized controlled single-center open-label study (clinicaltrials.gov NCT04560283); forty days after vaginal delivery or cesarean section, these women were randomized (ratio 1:1) to apply vaginal gel HYALOGYN® (HYDEAL-D® 2%; Fidia Farmaceutici, Abano Terme, Italy) every 3 days up for 12 consecutive weeks (T group) or to undergo expectant management (E group). Patients with evidence of vaginal infection were excluded. At baseline visit (V1) and at the end of treatment (V2), sexual function was assessed by the Female Sexual Function Index (FSFI) and dyspareunia severity at Visual Analogue Scale (VAS). The presence of postnatal depression was investigated by the Edinburgh Postnatal Depression Scale (EPDS). Vaginal pH and vaginal maturation indexed (VMI) were evaluated by an indicator dipstick and a vaginal swab, respectively. Treatment-related adverse events were collected.

Results

At baseline (V1), there were no significant differences in intensity of dyspareunia at VAS (p=0.192), total FSFI (p=0.701), and EPDS scores (p=0.192) between T and E groups. At V1 both groups had a similar mean pH value (5.4±2.4 vs. 5.1±2.5; p=0.192) and proportion of patients with VMI <50 (29.2% vs. 50.0%; p=0.140). At the end of the treatment (V2), a similar number of women had a regular sexual activity (p=0.312), although in T group there was a greater improvement of mean total FSFI (+ 17.0±9.3 vs. + 9.5±9.3; p<0.001) and dyspareunia at VAS (- 32.9±19.4 mm vs. - 15.5±19.4 mm; p=0.007). EPDS scores more significantly decreased in T than E group (- 2.8±3.0 vs. - 1.3±3.0; p<0.001). The analysis of vaginal status showed a mean lower pH (4.1±2.3 vs. 5.2±2.3; p=0.007) and a higher rate of VMI >65 in T group (69.2% vs. 30.8%; p=0.004). Only one patient (2.1%) experienced vaginal burning, but no patient discontinued the vaginal local therapy in T group.

Conclusions

Preliminary data analysis showed that the vaginal application of the Hydeal-D based gel (HYALOGYN®) may promote the restoration of sexual function in the postpartum period, lowering vaginal pH and ameliorating the estrogenic status of the vaginal epithelium.

The breast health and diseases

Ghrelin and aromatase expression in invasive breast cancer - variations to age and menopausal status

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Introduction

Breast cancer patients benefiting aromatase inhibitors are selected based on estrogen (ER) and progesterone (PgR) receptors statuses, instead of intratumor aromatase immunoreactivity. Main aromatase synthetis sites differ in fertile (ovary) vs. menopausal women (adipose tissue). As prevalence of obesity increasingly rises, frequently associating to breast cancer, ghrelin - an important weight regulator - may play a role in breast tumorigenesis processes.

Patients and methods

Using polyclonal antibody immunohistochemistry technique we assessed ghrelin and aromatase immunoreactivity (as intensity and/or percentage scores) in 70 tissue samples (containing tumor, stroma, adipose tissue) from breast cancer women (divided by age 55 into two subgroups: pre- and perimenopausal vs. postmenopausal, at the moment of surgery), and compared to current histopathological variables of breast carcinomas.

Results

Both aromatase and ghrelin expression in tumor cells were inversely correlated with tumor grading (ϱ=-0.361, p=0.027; ϱ=-0.449, p=0.020), and positively with ER (ϱ=0.143, p<0.001; ϱ=0.221, p=0.003). Dividind the study group by age, women aged <55y had both aromatase and ghrelin expression in tumor cells correlated strongly, stastistically significant, with ER (ϱ=0.410, p<0.001; ϱ=0.338, p=0.004), but not also women aged ≥55y (ϱ=0.131, p=0.899; ϱ=0.174, p=0.851). Although levels of statistical significance were not reached (p=0.1-0.3), negative associations between aromatase and fibrocystic breast disease (ϱ=-0.342), tumor grading (ϱ=-0.385, tubular differentiation ϱ=-0.414), PgR (ϱ=-0.224), and Ki67 (ϱ=-0.222), and a positive association with lymph node invasion (ϱ=0.337) were observed in women <55y, while women ≥55y had weaker inverse correlations with only tumor grading (ϱ=-0.347) parameters and Ki67 index (ϱ=-0.133). Ghrelin was also inversely correlated with tumor grading (ϱ=-0.449, tubular differentiation ϱ=-0.277, nuclear polymorphysm ϱ=-0.391).

Conclusions

Breast cancer tumor cells express ghrelin and aromatase. Aromatase positively associated with ER in women <55y, suggesting the importance of local breast estrogen synthesis in fertile women. After menopause, other estrogen pathways may contribute greater to local estrogen production, than aromatase mediated pathway. Both ghrelin and aromatase immunoreactivity inversely associated with cell differentiation and proliferation tumor markers suggesting a possible positive prognostic value.

The breast health and diseases

Season-depended reference values of antioxidants in blood serum of healthy women of reproductive age without benign breast disease

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Introduction
Oxidative stress is known as one of the important mechanisms for the development of endocrine dysfunction, reproductive disorders and benign breast disease. Nevertheless, there is a lack of data regarding reference values of antioxidant system parameters in women of reproductive age.

Objective
To determine the reference values of antioxidants in blood serum of healthy reproductive aged women, depending on seasons of sampling.

Methods
The 'super-control' group consisted of 18-45 years old healthy women, identified among the unselected population, recruited during the institution-based, cross-sectional study in 2016-2019. Of the 1555 women of reproductive age studied, 153 were selected as 'super-controls' according to the following criteria: a) subjects with written informed consent; b) with menstrual cycle length 21-34 days. Exclusion criteria included: a) current pregnancy or lactation; b) history of hysterectomy, bilateral oophorectomy, endometrial ablation, and or uterine artery embolization; c) current or previous (within 3 mos.) hormonal medications intake; d) PCOS, e) hyperprolactinemia, f) hypothyrosis, g) NCAH, h) history of chronic disease; i) a body mass index ≥30 kg/M2 and j) benign breast disease. Serum samples of 'supercontrols' were analyzed for total antioxidant activity (TAA), superoxide dismutase (SOD), α-tocopherol, retinol, reduced and oxidized glutathione (GSH/GSSG) using spectrofluorometry and spectrophotometry. We defined the reference values for antioxidants as the 5-95th percentile. The study was approved by the local ethics committee.

Results
The 5-95 percentile for all studied parameters for Summer-Autumn season were found as follows: TAA 10.46-19.44 units, SOD 1.35-1.87 units, GSSG 1.85-3.04 mM/l, GSH 1.41-2.44 mM/l, retinol 0.36-1.06 μM/l, α-tocopherol 4.21-13.44 μM/l. Reference ranges for Winter-Spring season were the following: TAA 10.08-16.94 units, SOD 1.41-1.85 units, GSSG 2.08-3.25 mM/l, GSH 1.64-2 52 mM/l, retinol 0.39-1.09 μM/l, α-tocopherol 5.31-10.34 μM/l. It was also shown that values of TAA in blood serum with sampling during the Summer-Autumn season were significantly higher if compared to ones in the Winter-Spring season.

Conclusions
Some of the reference ranges of antioxidant system parameters in healthy women without benign breast disease depend on the seasonal period of blood collection.

The breast health and diseases

Cytoskeleton rearrangement and migration of MCF-7 breast cancer cells stimulated by prolactin

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Context

Breast cancer is one of the greatest female health concerns given the high index of morbimortality. Great strides have been made in acquiring knowledge of the molecular biology of cancer for the development of new therapies to help control the disease. However, in the presence of cell migration to other tissues (metastasis), treatments lose their efficacy and prognosis often worsens.

Objective

Determine the effects of prolactin in the cell migration, actin rearrangement, and modulation of the cytoskeleton in MCF-7 breast cancer cells.

Methods

The cells were cultured in 6 well dishes with supplemented medium and then divided into 4 different assays: Assay1 (MCF-7-control); Assay2 (MCF-7+25ng/ml of prolactin); Assay3 (MCF-7+50ng/ml of prolactin) and Assay4 (MCF-7+100ng/ml of prolactin). The migration analysis, as well the immunoblotting evaluation of Focal Adhesion Kinase (FAK) and Membrane-Organizing Extension Spike Protein (Moesin), were performed 24 hours after the treatment. The actins' cytoskeleton modulation were analyzed, by immunofluorescence, 30 minutes after the treatment.

Results

Data showed that prolactin, in Assay3 (50 ng/ml) and Assay4 (100 ng/ml), enhanced the migration of MCF-7cells. Furthermore, the expression of FAK and Moesin, as well as the cell membrane thickness, were increased in those Assays ($p<0,001$).

Conclusions

In summary, prolactin enhanced MCF-7 breast cancer cell motility. This result is probably related to the activation of Actin adjustment on the cytoskeleton and formation of focal adhesion complexes. Our findings may extend the knowledge about the physiological and pathological processes associated with prolactin and cell motility, nevertheless, further studies are necessary to better understand these correlations.

The breast health and diseases

Prevalence, characteristics, and outcome of familial breast cancer

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Context

The 15-20% of patients affected by breast cancer have a family history of breast and/or ovarian cancer, but only 5% of the same population are carriers of a hereditary mutation predisposing to this type of disease.

Objective

The aim of this study was to compare patients with or without a gene mutation in our population.

Methods

We collected retrospective data relating to all the patients operated between 2002 and 2018 and subjected to genetic tests in search of mutations for the BrCa1 and 2 genes. We took into consideration the characteristics of the patients, of the tumors, and the treatments performed. Then the population was divided according to the presence of mutations for the BrCa1 and 2 gene.

Results

105 patients underwent genetic testing. 20% were carriers of BrCa1 mutation, 28% of BrCa2, 45% negative for mutations, and the remaining 7% bear mutations of uncertain significance. With respect to the general population, the tested patients were significantly younger (46 vs 61 years) and had more frequent triple-negative tumors (24% vs 8%), high grade (55% vs 28%) and Mib1> 20% (66% vs 38%) ($p < 0.05$). In 44% of cases the diagnosis was made by physical examination, and patients with gene mutations had an increased risk of developing second neoplasms, mostly mammary and ovarian. Prophylactic mastectomy and ovairectomy was respectively performed in 24% and 14% of the mutated BrCa1, 35% and 10% of the mutated BrCa2, and 5% of the patients not mutated but with important familial history.

Conclusions

In our population the genetic test was positive for mutations in half the cases, demonstrating the effective selection of the patients subjected to the test. Almost a third of the patients tested had a mutation in the BrCa2 gene. As expected, among patients undergoing genetic testing the diagnosis was mostly autopalatory because the young age did not allow their inclusion in screening programs. About one third of mutated patients underwent prophylactic surgery, as well as a minority of unmutated patients, motivated by a strong familiarity.

The breast health and diseases

Extended adjuvant ET in a real-life retrospective cohort of CTS5-stratified HR+ breast cancer patients: is it beneficial for everyone?

Andrea Villasco (IT), Francesca Agnelli (IT), Marta D'Alonzo (IT), Nicoletta Biglia (IT)
Mauriziano Umberto I - Università degli studi di Torino

Context
To date, 5 years of adjuvant endocrine therapy (ET) is the standard treatment for patients with hormone receptor-positive (HR+) cancers; however, more than 50% of distant recurrences (DR) will develop after this time. Extension of ET has been shown to improve DFS and OS but is burdened with more therapy related side effects. Selecting the patients at higher DR risk, who could benefit most from an extended regimen, has thus become a rising need. The Clinical Treatment Score at 5 years (CTS5) is a prognostic tool, created and validated on the ATAC and BIG1-98 cohorts of postmenopausal patients, which uses clinicopathological data to estimate DR risk after 5 years of adjuvant ET for HR+ breast cancer.

Objective
To evaluate the effect of an extended adjuvant ET in a cohort of real-life pre/postmenopausal patients diagnosed with HR+ breast cancer whose late distant recurrence (LDR) risk has been assessed with CTS5.

Methods
CTS5 was calculated retrospectively for all patients. For each CTS5 risk class, the extended ET subgroup was compared to the standard ET one. Survival analysis was performed with the Kaplan Meier method. Hazard ratios were obtained with Cox regression and reported with CI95%.

Patients
784 patients diagnosed with HR+ tumors at Umberto I Hospital of Turin between 1988 and 2014 and DR free after 5 years of ET were enrolled for this analysis.

Intervention
Tailoring extended adjuvant ET prescription on CTS5 prognostic stratification.

Main outcome measure
The primary endpoint of this study was LDR rate.

Results
Median follow up was 8,01 years (5-26). According to CTS5 score, the 784 patients were categorized as follows: 283 (36%) low risk, 232 (29,5%) intermediate risk, 269 (34,5%) high risk. An extended adjuvant ET was prescribed in 15%, 22,8% and 31,6% of cases respectively (p<0,001). For these patients, median duration of ET was 7 years (6-10). No significant differences in terms of LDR could be observed between extended ET and standard ET in the low and intermediate risk subgroups (2,3% vs 4,5%, p=0,7; 7,5% vs 7,2%, p=1,00 respectively).
In the high risk subgroup, LDR rate was significantly lower in the patients who underwent extended ET compared to standard ET (5,88% vs 16,84%, p=0,01), the former treatment conferring an LDR risk more than halved than the latter (HR 0,41, CI95%: 0,15-1,07).

Conclusions
Prognostic stratification of CTS5 identifies high risk patients for whom an extended adjuvant ET appears to lower the LDR rate.

The breast health and diseases

Validation of CTS5 on a retrospective cohort of real-life pre and postmenopausal patients diagnosed with HR+ breast cancer: is it prognostic?

Andrea Villasco (IT), Francesca Agnelli (IT), Marta D'Alonzo (IT), Nicoletta Biglia (IT)
Mauriziano Umberto I - Università degli studi di Torino

Context
To date, 5 years of adjuvant endocrine therapy (ET) is the standard treatment for patients with hormone receptor-positive (HR+) cancers; however, more than 50% of distant recurrences (DR) will develop after this time. Extension of ET has been shown to improve DFS and OS but is burdened with more therapy related side effects. Selecting the patients at higher DR risk who could benefit from an extended regimen has thus become a rising need. The Clinical Treatment Score at 5 years (CTS5) is a prognostic tool, created and validated on the ATAC and BIG1-98 cohorts of postmenopausal patients, which uses clinicopathological data to estimate DR risk after 5 years of adjuvant ET for HR+ breast cancer.

Objective
To validate the prognostic value of CTS5 in a cohort of real-life pre/postmenopausal patients diagnosed with HR+ breast cancer.

Methods
CTS5 was calculated retrospectively for each patient. Patients were analyzed separately according to menopausal status. Survival analysis was performed with the Kaplan Meier method. Hazard ratios were calculated with Cox regression and reported with 95% CI.

Patients
603 patients diagnosed with HR+ tumors at Umberto I Hospital of Turin between 1988 and 2014 and DR free after 5 years of ET were enrolled for this analysis.

Intervention
Utilization of CTS5 as a mean to tailor the prescription of extended ET by selecting patients at high risk of developing a late distant recurrence (LDR).

Main outcome measure
The primary endpoint of this study was LDR rate.

Result
Median follow up was 7,89 years (5-26). According to CTS5, the 426 postmenopausal women were categorized as follows: 152 low risk, 139 intermediate risk, 135 high risk. LDR rate was 3.94%, 7,19% and 15,55% respectively ($p<0,001$). At Cox regression analysis, CTS5 resulted significantly prognostic for LDR: patients with high CTS5 score showed a fourfold risk of developing an LDR when compared to patients with low CTS5 score (HR 4,22, CI95% 1,70-10,4). The same analysis was conducted for the 177 premenopausal women: 88 were classified as low risk, 40 as intermediate risk, 49 as high risk. LDR rate was 5,6%, 7,5% and 20,4% respectively ($p<0,001$), with the high-risk subgroup having a threefold risk of developing an LDR than the low risk one (HR 3,36, CI95% 1,04-10,86).

Conclusions
CTS5 proved to be prognostic for LDR in real life patients including premenopausal women and should be considered in routine practice for prescribing extended ET.

The breast health and diseases

Modern management of organic nipple discharge

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Objective

To present the diagnosis tools: ductogaphy MRI MRIductography duct ultrasonography and ductoscopy with duct lavage and brushing in the diagnosis of organic nipple discharge.

Method

Imagery is performed first to localize the lesion in the pathological duct. The direct visualization of the lesion is possible by ductoscopy. The microendoscope is inserted in the pathological duct after gentle dilatation under a saline perfusion and a duct lavage cytology with duct brushing allow a cytological diagnosis.

Results

Navigation in the ducts recognizes suspicious lesions: papilloma, duct ectasia, neoplasma, microcalcifications. The lesion is categorized in accordance with international classifications as superficial, elevated or multiple (Makita). Mammary pump (Zervoudis), duct brushing (Beechey), and liquid cytology increase the quantity and the quality of the cytology specimen. Moreover, the dosage of hormonal receptors, cerb-B2, tumor markers CA 15.3, CEA, as well as the new biomarkers: DNA methylation and immnoglobulins (De Groot), could complete the diagnosis for the management.

Discussion

The accuracy of MRIgalactography is high but do not visualize directly the lesion neither the benignity of malignancy. Ductoscopy with duct sampling cytology sensitivity vary in the literature but is high in expert centers (> 88% Dietz). Autofluorescence ductosopy improves the quality of the image for the diagnosis. Ductoscopic biopsy with microforceps, vacuum assisted biopsy (Hunerbein), and ductoscopic extraction (Feldman) provide tissue specimen of the lesion with higher sensitivity and specificity. Interventional ductoscopy with microwaves, laser, and ductoscopic assisted microdolichectomy are elective microsurgical procedures.

Conclusions

Ductoscopy with duct lavage and brushing as cyto-histologic sampling are good techniques to explore organic nipple discharge. Moreover interventional ductoscopy could perform the treatment in case of benign lesion.

Pre-neoplastic and neoplastic diseases

Local immune status in chronic cervicitis of a nonspecific etiology

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TGU named G.R.Derzhavina

The frequency rate of cervicitis is about 60-70%. The inflammatory process may appear both in local and systemic changes with the participation of various inflammatory markers including cytokines. When interacting around each other, cytokines form a cytokine net which defines the characteristics of a local immune response or immune regulatory processes state at a cell structure stage, especially, an uterine cervix mucosa.

Aim

To develop a personalized approach to the management of patients with chronic cervicitis using molecular genetic markers.

Materials and methods

We studied cytokines (IL-1β, IL-4, IL-6, IL-8, IFN-y, TNF-α) in a local immune of lower genital tracts of 83 women with chronic cervicitis. The control group comprised 35 apparently healthy women. In order to specify the diagnosis all women underwent complex examination which included clinical and anamnestic study, microscopy of vaginal smear using PCR-method (Femoflor 16, PCR 7 (pathogenic germs), genetic polymorphisms detection (IL-1β, IL-4, IL-6, IL-8, IFN-y, TNF-α).

Results and discussion

As follows from the statistical analysis of the healthy women from the control group, the expression of the cytokines comprised: IL-1β =51.6; IL-4=28.3; IL-6=42.1; IL-8=302.3; IFN-y= 2.6; TNF-α=2.7. Within the group of women with a chronic cervicitis the expression of the cytokines was: IL-1β =97.2; IL-4=63.3; IL-6=84.5; IL-8=498.2; IFN-y=5.8; TNF-α=3.6. Two-fold increase in IL-1β concentration in comparison with the control group manifests the activation of stroma monocytes/macrophages affected by the inflammatory process. The increase in IL-6 concentration in an uterine cervix mucosa in women with chronic cervicitis shows high activity in monocyte-macrophage lineage of an immune response. The rising in IL-4 concentration in the study groups demonstrated statistically significant increase of this maker. The expression of this cytokine in patients with active inflammatory process was three times higher in comparison with the control group. Higher production of IFN-γ results in the activation of macrophages within the abnormal focus.

Conclusion

All the women patients suffered from chronic cervicitis had the increased level of cytokines responsible for maintaining the optimal level of cell activity. Under physiological conditions the production of pro- and anti-inflammatory cytokines is crucial for maintaining the antibacterial defense of the cervix uteri in the ready mode.

Pre-neoplastic and neoplastic diseases

Pregnancy in patients with thyroid cancer - individualized follow-up

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University of Medicine and Pharmacy Victor Babes Timisoara

Context

Thyroid cancer is the most common endocrine malignancy and it can impair the course of a pregnancy.

Objective

We are presenting 10 cases of pregnant women with a history of thyroid cancer, with individualized approach for each case.

Methods

Retrospective study of thyroid cancer cases diagnosed in young females prior to pregnancy.

Patients

10 cases with diagnosed and treated thyroid cancer before pregnancy are presented. Each case has the particularities of individualized treatment during the entire pregnancy and postpartum. Mean age of the study group was 31±1.4 years, with mean diagnosis lag time of 4.5 years (2-7 years). All patients have undergone surgery and all were under suppressive supplemental therapy - with low TSH and normal fT4 values. Seven out of the ten patients have had previous radioactive iodine treatment. All these cases had the last radioiodine dose at least 2 years prior to pregnancy.

Intervention

After the confirmation of pregnancy, the thyroxin treatment doses were tapered in respect to the need of the pregnant women in order to acheive fT3 and fT4 values within the normal range, with TSH value in the range recommended for each trimester of pregnancy. Two cases previously treated with combined preparation were switched to thyroxin-only supplementation.

Main outcome measures

Clinical follow-up and fT3, fT4 evaluation. Pregnancy outcomes were followed: Apgar score, weight, length were assessed for each birth and TSH, fT4 on the 3rd day after delivery.

Restults

All 10 cases evolved with living birth, with one prematurity case. No significant differences were observed in the neonates compared to gestational-age-peers, born from mothers with no history of thyroid disease. Maternal thyroid outcome was evaluated in the first month postpartum by means of ultrasound, measurement of TSH, fT4, thyroglobulin and anti-thyroglobulin antibodies.

Conclusion

Changing the suppressive treatment, needed before pregnancy to supplemental treatment, during the entire time of pregnancy, did not seem to induce any maternal or fetal/neonatal complications.

Pre-neoplastic and neoplastic diseases

High Risk HPV (HR-HPV) viral load in coupled cytological and urine samples from women affected by Cervical Intraepithelial Neoplasia (CIN)

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Evaluation of the prognostic role of HR-HPV viral load in women undergoing to conization for biopsy evaluation of high grade of CIN and the evaluation of urine as surrogate of cytological samples for the evaluation of High Risk HPV (HR-HPV) viral load and

Patients

Two hundreds and sixty-nine patients were enrolled. Thirty milliliters of urine and cytological cervical samples were collected before surgical treatment.

Methods

The HR-HPV load was evaluated by HC2 (Qiagen). Statistically significant differences were determined using Mann-Whitney U test and Chi-square test or Fisher's exact test

Result(s)

The viral load had a different distribution depending on CIN grade: both considering CIN1, CIN2, CIN3, MIC, than CIN1 vs CIN>1, $p < 0.001$.
The urine HR-HPV load was lower (10 time less) in comparison with cervical samples.
There was no a correlation between viral load in the urine and corresponding cytological samples.
Nevertheless, a tendency of urine viral load depending on CIN was observed. The evaluation on the same sample of urine and cervical viral load showed a statistically significant distribution depending on CIN grade (CIN1 vs CIN>1, $p < 0.001$)

Conclusions

The viral load may represent a new prognostic tools for the evaluation of infection. A lower viral load was observed in CIN1 in comparison to CIN>1 in urine and cytological samples, focus on the changing of CIN evolution between biopsy to surgery and suggesting that a analytical step for the evaluation of CIN grade should be performed before conization 8about 6-8 months after histological evaluation of biopsy).
Moreover, these data suggest that urine may represent a surrogate of cytological sampling, even if the analytical and pre-analytical procedure, starting from urine sample collection to instrument (HC2) sensitivity should be implemented. Indeed, urine may represent a non-invasive procedure of collection and could be used as not disconfortable procedure to monitoring the evolution of CIN in order to avoid overtreatment mainly in young women, taking into consideration the collateral effect of outcome in pregnancy for patients undergoing to conization.

Pre-neoplastic and neoplastic diseases

Efficacy and safety of a local environment modifying vaginal gel on Cervical Intraepithelial Neoplasia 1 and 2, on high-risk HPV, and on p16 - Comparison with the classical “watch and wait” approach: a randomized controlled trial

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Objective

There is yet no single validated non-surgical therapeutic approach for mild to moderate cervical intraepithelial neoplasia (CIN1 and 2). The present randomized clinical trial aimed to study the effect of such a treatment with SAM vaginal gel on histologically-proven CIN2 as well as p16 positive CIN1, and presence of the oncomarker p16. SAM vaginal gel is a medical device containing adsorptive silicon dioxide and an antioxidative citric acid / selenium combination.

Material and methods

216 women aged 25-60 years participated in this study at three colposcopy centres. They were randomised either to receive an intravaginal daily dose of SAM gel for three 28-days periods, or be followed-up clinically without intervention, corresponding to gynaecological guidelines.

The main outcome was efficacy, defined as a combined histological and cytological regression. At baseline and at 3 months all participants had: a colposcopy, with IHC p16 test of guided biopsies of visible lesions; a cervical smear for cytology, hr-HPV and p16/Ki-67 (CINtec® Plus) test; and a blood sampling for Selenium analysis. At 6 months they had a cervical smear for cytology and p16/Ki-67 (CINtec® Plus) test only.

Results

Regression of CIN lesions was observed in 78 out of 108 patients (72.2%) in the SAM gel arm, whereas a similar finding was seen only in 27 out of 108 patients (25.0%) in the control arm. Similarly, the change in the p16/Ki-67 cytological test status was significant in favour of the treatment group. The prevalence of high-risk (hr) HPV on the cervical smear decreased significantly in the treatment group, from 87.0% to 39.8%, while it slightly increased in the control group, from 78.7 % to 83.3%. At 6 months, i.e. 3 months after the end of treatment, the effect of the treatment sustained mainly in ASCUS and LSIL. Adverse events related to the treatment were temporary and none of them required the termination of SAM gel application.

Conclusions

SAM vaginal gel enhances the regression of cervical lesions and clears hr-HPV and p16/Ki-67 significantly.

Pre-neoplastic and neoplastic diseases

Erbium laser treatment of episiotomy-related complaints – 1 year follow-up

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Objective
Episiotomies have often adverse effects like are: infections, increased pain and bleeding, prolonged healing times, scarring, increased discomfort during intercourse. Many of these symptoms are persisting for years after the surgery and could significantly influence the patients' quality of life. Ablative lasers (full spot and fractional) are widely used in aesthetics and dermatology to reduce the scars visibility and to improve the functionality of the scarred part of the body. The purpose of this study was to evaluate efficacy and safety of erbium laser treatment for the range of long-term episiotomy scars-related symptoms.

Methods
This single center prospective study was performed in the period from September 2017 to March 2019 on a group of patients with episiotomies complaining to: painful intercourse, pain while sitting, pain at pressure, pulling, bumps at perineum and bleeding after intercourse. Patients were treated with ablative ErYAG laser in two steps protocol: full spot (2 mm) cold ablation along the scar with 300 mJ and 0.1 msec pulses, follow by fractional beam (5 mm spot, 800 mJ and 0.6 msec) across the whole episiotomy surface with 2 cm margins. Three sessions were performed with one month intervals. Subjective patients' assessment of improvement was measured with 11 point numerical scale (0-10). Treatment discomfort was measured with VAS (0-10). Follow-ups were performed at each visit and at 12 months after the last laser treatment. Adverse events were registered at every follow-up.

Results
110 female patients were included in this study. Average age was 40.7 years (range: 24-56) gravidity 2.0 (1-4) and parity 1.7 (1-3). Average time from episiotomy surgery was 3.7 years (range: 1-15). Majority of the patients (96 patients or 87.3%) suffered from more than one of six observed symptoms. All patients improved their symptoms and 45.5 % claimed that after three sessions they have no more complaints. At 1 year follow-up 51.8% of patients were free of symptoms and have no more complaints. Average improvements on numerical scale scores were 4.9 after the first session, 7.4 after the second and 8.9 after the third session. At one year follow-up the average improvement was 9.1. Average pain during the procedure (without anesthesia) was 5.4/10. Considering the short duration of treatment (around 2 minutes) all patients tolerated the treatment very well. All reported adverse effects were mild and transient.

Conclusions
Erbium laser treatment showed efficacy in improvement of symptoms connected with episiotomy scars with no major adverse effects noted. Patients' tolerated the treatment well and their satisfaction was very high. Treatment effects last at least 12 months.

Pre-neoplastic and neoplastic diseases

Frequency of symptoms of genitourinary syndrome of menopause in Colombian Afrodescendant women. Assessment using the vulvovaginal symptoms questionnaire

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Context
Genitourinary Syndrome of Menopause (GSM) must be assessed in different communities and it is important to take into account their ethnicity.

Objectives
To estimate the frequency of symptoms of GSM in climacteric afrodescendant women from Colombian Caribbean, and to estimate their association with the menopause status.

Methods
Cross-sectional study which is part of the investigation project CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas). Anonymous and voluntary participation, approved by the ethics committee of Universidad de Cartagena, Colombia. Epiinfo-7 was used. Quantitative variables are presented in means and standard deviation, qualitative ones in absolute values and percentages. Not adjusted logistic regression was used: each item of the Vulvovaginal Symptoms Questionnaire (VSQ) was taken as the dependent variable and the menopause status as the independent variable.

Patients
Afrodescendant women from the Colombian Caribbean, with ages between 40-59 years old, healthy, enlisted by pollsters in their places of residence.

Intervention
A form of the sociodemographic characteristics and the VSQ, were applied.

Meassure of the primary outcome
Symptoms that are part of the GSM.

Results
369 women were studied. The mean age was 49.1±5.8, premenopausal 191 (51.8%) and postmenopausal 178 (48.2%), of which 66.3% were in an early stage and 33.7% in a late stage. Body mass index: 27.9 ± 5.4, with sexual activity 86.2%, sexual intercourse per week: 2.0 ± 1.9, couple's age: 41.9 ± 22.2 years. 25% reported that vulvar symptoms caused dryness during sexual activity, 16% vulvar irritation, 12% vulvar pruritus, 4% worry about symptoms and 3% considered that the symptoms affected the desire to be with other people. 15% had one or two symptoms and 8% had three or more. Postmenopause, as well as the early and late stages, were significantly associated with vulvar symptoms causing dryness during sexual activity, with respect to premenopause, OR: 5.5 [95% CI: 3.2-9.5], OR: 3.1 [95%CI: 1.9-5.1] and OR: 2.3 [95% CI: 1.3-4.1], respectively. No association of menopausal status was observed with the other items of the VSQ (p> 0.05).

Conclusions
The most frequent manifestations were: vulvar symptoms causing dryness during sexual activity and vulvar irritation. Postmenopause in relation to premenopause, was associated with five times greater presence of vulvar symptoms causing dryness during sexual activity.

Pre-neoplastic and neoplastic diseases

Randomized, prospective trial to evaluate the effects of the intravaginal gel DeflaGyn® on the regression rate of HPV high-risk positive strains and the cytological p16/Ki67 marker in women with cytological findings according to Bethesda (ASC-US, LSIL, AS)

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Objective
The objective of the study was to determine the influence of a medical device containing silicon dioxide, citric acid and selenite in women with cytological findings according to Bethesda (ASC-US, LSIL, ASC-H, and HSIL) on the clearance of HPV high-risk strains. The other objective was the evaluation in the changes of positive cytological tests for p16/Ki67 after a 3-months treatment as well as after a further 3-months follow-up.

Material and Methods
Two-hundred and six teen (216) patients were randomized in an open, prospective study. One hundred and eight (108) received a medical device containing silicon dioxide, citric acid and selenite, and 108 conformed a placebo group. The vaginal gel was applied every day for over three months.
Before and after the treatment, the HPV status and the p16/Ki67 status were determined in all 216 patients.

Results
After the 3-month treatment a clearance of High-risk positive HPV patients from 94 to 43 (reduction from 89.7% to 39.8 %) was observed in the active arm whereas in the control arm 85 patients were positive at the screening stage and 90 after 3 months (elevation from 78.7% to 83.3 %). Under those which had received a vaccination 10 women were tested positive before treatment in the active arm and 12 in the control arm.
Regarding the CINtec Plus test p16/Ki67 at screening, 77 patients were positive in the active arm and 99 in the control arm (71.3% and 91.7 % respectively). After the treatment of 3 months, only 13 (12%) were positive in the active arm and still 81 (75.0%) in the control arm. Three months after finishing treatment, only six patients (5.7 %) were positive in the active arm, whereas 82 (75.2%) patients remained positive in the control arm.

Conclusion
DeflaGyn® Vaginal Gel has shown to be highly effective in the reduction of HPV high risk and p16/Ki67 positive women with cytological findings according to Bethesda ASC-US, LSIL, ASC-H, and HSIL, thus offering a new active management in the prevention of cervical cancer.

Pre-neoplastic and neoplastic diseases

The therapeutic effect of nigella sativa extract on female wistar rats vaginal candidiasis model

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Background

Candidiasis is the most common fungal infection of humans caused by Candida albicans. Immediate and proper management of vaginitis candida must be done to prevent complications. Nigella sativa has pharmacological effects as antimicrobial, anti-inflammatory, immune stimulation and anti-cancer properties. Nigella sativa was proven have antifungal effect *in vitro*, and this study was to assess antifungal and possible therapeutic effect *in vivo*.

Methods

This study was an analytic study which assess the therapeutic effect of Nigella sativa in rats vaginal candidiasis model. The subject were 28 rats that had been inoculated with Candida albicans and divided into 4 groups: Nigella sativa group, fluconazole group, combination of Nigella sativa with fluconazole group and control group. Candida albicans colony was measured to assess the therapeutic effect of the treatment.

Results

There were no difference number of Candida albicans colony between all group before inoculation (p = 0,274) and after inoculation (p = 0,323). There were significant decreased number of Candida albicans colony on the 24 hours after the treatment between the three types of treatment with the control group (Nigella sativa group p = 0,046; Fluconazole group p = 0,002; Nigella sativa + fluconazole p = 0,002)

Conclusion

There was therapeutic effect of Nigella sativa by reducing the number of Candida albicans colonies.

Keywords: Fungal Inoculation, Pseudoestrus, Candida albicans, Nigella sativa, Vaginal Candidiasis, Fluconazole

Pre-neoplastic and neoplastic diseases

How postoperative time effects pregnancy outcomes after cervical conization

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Objective
To investigate the relationship between postoperative time and pregnancy outcomes after cervical conization (include Leep and CKC).

Methods
Observational analytical study with a sample of pregnant women, who have history of the Leep and CKC during the period of January 2016-March 2019. When objects were registered in obstetrics, they were backtracked the general situation, previous operation cases; then objects were monitoring their following pregnancies. To analysis the influence of postoperative time and operative methods on the pregnancy outcomes after cervical conization.

Results
In the Leep group, the pregnancy outcomes of those four groups at different intervals were compared: the abortion rate, preterm birth rate, premature rupture rate of membranes, and duration of premature rupture of membranes were not affected ($P > 0.05$). In CKC group, the pregnancy outcomes of those four groups at different intervals were compared: the group of interval 2.9 to 8 months was significantly higher than other groups in preterm birth rates, which the difference was statistically significant ($P < 0.05$). While the rate of miscarriage, premature rupture rate of membranes, duration of premature rupture of membranes were not affected by postoperative time, which there was no statistically significant difference ($P > 0.05$). In the binary logistic regression model, the probability of miscarriage caused by CKC was 6.042 times higher than that caused by Leep (OR=6.042, P=0.018,95%Cl 0.668~54.678). In ROC curve analysis the cut-off value of Leep group was 4.75 months. The incidence of severe preterm birth and miscarriage in the postoperative time > 4.750 months group was lower than which <4.75 months. The cut-off value of the CKC group was 13.75 months. The incidence of severe preterm birth and miscarriage in the postoperative time > 13.75 months group was lower than which <13.750 months, with a statistically significant difference (P=0.034).

Conclusion
Pregnancy in too short time after Leep surgery will increase the incidence of abortion, while pregnancy in too short time after CKC surgery will increase the incidence of pre-term birth. Compared that of CKC, pregnancy after Leep is safer and requires shorter interval. Therefore, for patients with fertility needs, appropriate surgical method should be selected, the timing of postoperative pregnancy should be concerned, and the monitoring and appropriate treatment in pregnancy period should be strengthened to reduce the occurrence of postoperative adverse pregnancy outcomes.

Gynecological oncology

miR-145-5p expression can be useful for uterine fibroids and leiomyosarcoma differential diagnosis

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Introduction

Uterine smooth muscle tumors are the most frequently occurring type of gynecological mesenchymal tumor and can be classified as benign (leiomyomas - LM) or malignant (leiomyosarcomas - LMS). These tumors share morphological and molecular characteristics that difficult their differential diagnosis. miR-145-5p expression evaluation may be useful in identifying these tumors and consequently in improving clinical outcomes.

Objective

To evaluate the miR-145-5p expression profile in uterine leiomyoma and leiomyosarcoma cell lines and patients´ samples; to identify (potential or predictors) target genes by in silico analysis.

Methods

ULM (THESCs CRL-4003) and ULMS (SK-UT-1 HTB-114) cell lines were purchased from the American Type Tissue Collection (ATCC); cells were seeded in 75 cm^2 bottles in DMEM/F-12-D2906-10L (Sigma-Aldrich) and Basal Medium Eagle-B9638-10X (Sigma-Aldrich), respectively, and supplemented with 10% of fetal bovine serum (FBS). Thirty-nine formalin-fixed paraffin-embedded (FFPE) women samples were obtained from Molecular and Structural Gynecology Laboratory of University of Sao Paulo Medical School (FMUSP). MicroRNAs were extracted from all cell lines using the mirVana™ miRNA Isolation-kit (Ambion). The FFPE patients' samples were extracted with ReliaPrep™ FFPE Total RNA Miniprep System (Promega). Quantitative Real-Time PCR (qRT-PCR) was carried out using the miScript SYBR® Green PCR-kit with MIHS-109ZA-Qiagen 96 wells plate (Qiagen). All data were normalized and submitted to statistical analyses. In silico analysis were performed using software miRTargetLink software.

Results

miR-145-5p showed a lower expression in LMS compared to LM, using myometrium cell reference, in both cell lines (Fold Regulation [FR] LM: 2.33 and LMS: -10.0) and tumor samples and (FR LM: -2.68 and LMS: -8.64). In silico analyses showed that many genes associated with cancer pathways are regulated by this microRNA, such as NRAS, HMGA2, SOX2, MYC and CDK6.

Conclusions

Our results showed miR-145-5p differential expression profile between LM and LMS cell lines and patients´samples. Future analyses will be performed focusing on circulating miRNAs. These studies will help inform the preoperative diagnosis of LM and LMS, contributing significantly to the selection of surgery cases.

Gynecological oncology

miR-186-5p overexpression may predict the malignancy risk in uterine smooth muscle tumors

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Introduction

Uterine smooth muscle tumors (USMTs) are neoplasms that range from benign leiomyomas (LM) to high-grade leiomyosarcomas (LMS). MicroRNAs (miRNA) are a group of small noncoding RNAs that are relatively specific for histologic and tumor cell types. Some of them can act as tumor-inducing miRNAs, referred to as oncomiRs. Several biological processes in human cancer are affected by miR-186, but in USMTs the role and underlying mechanism of miR-186-5p remain unknown.

Objective

To investigate the expression profile of miR-186-5p in LM and LMS cell lines and patients' samples and to identify the network of potential target genes.

Methods

39 formalin-fixed paraffin-embedded (FFPE) women samples were obtained from the Molecular and Structural Gynecology Laboratory of University of Sao Paulo Medical School (FMUSP). LM (THESCs CRL-4003) and LMS (SK-UT-1 HTB-114) cell lines were cultured in specific medium and conditions according to ATCC. MiRNAs were extracted from cell lines and FFPE samples. Quantitative Real-Time PCR (qRT-PCR) was carried out using the miScript SYBR® Green PCR (Qiagen) detection system. All data were normalized using SNORD61 and SNORD68 and analyzed by ΔΔCt method. In silico analysis were performed with the miRTargetLink software.

Results

We found a higher expression of miR-186-5p in LMS cells (Fold Regulation [FR] 1.57) compared to LM (FR -7.46), and patients' samples (FR LM -24.11and LMS 27.39). In addition, in silico analysis indicated that this molecule acts as an oncomiR in LMS by targeting FOXO1, AKAP12 and NCSTN.

Conclusions

Our results showed that miR-186-5p has different expression profiles in LM and LMS. The overexpression indicates that this miRNA may act as an oncomiR in LMS and presents a potential role in LMS development and potential targets for its treatment.

Gynecological oncology

INSR and IRS1 regulation by microRNA in uterine smooth muscle tumor cells

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Introduction

Uterine leiomyoma (LM) also called uterine fibroid is the most common benign uterine smooth muscle tumors (USMT). In contrast, uterine leiomyosarcoma (LMS) occurs with lower frequency but higher recurrence, metastasis, and mortality rates. Studies that evaluate microRNA (miRNA) expression have been shown to be important in many cancers. The evaluation of these molecules and insulin pathway target genes (INSR and IRS1) may help to provide additional insights into the LMS progression and possible new therapeutic approaches.

Objectives

To evaluate 26b-5p, 7-5p, 152-3p, 195-5p, 15b-5p, 148a-3p and 96-5p miRNAs and their targets INSR and IRS1 in LM and LMS cell lines.

Methods

LM (THESCs CRL-4003) and LMS (SK-UT-1 HTB-114) cell lines were purchased from the American Type Tissue Collection (ATCC). miRNAs were extracted from all cell lines and the cDNA synthesis were carried out. Quantitative Real-Time PCR (qRT-PCR) was carried out using the miScript SYBR® Green PCR-kit with MIHS-109ZA-Qiagen 96 wells plate (Qiagen) for microRNA expression evaluation and and TaqMan Gene Expression Assay (Applied Biosystems) for INSR and IRS1 gene expression analysis. Molecular results were submitted to statistical analyses. In silico analysis were performed by miRTargetLink software.

Results

26b-5p, 195-5p, 15b-5p were overexpressed in LM cell line (Fold Regulation - FR: 3.08, 2.13 and 1.88 respectively). Already 7-5p, 148a-3p and 96-5p were downreagulated in these cells (FR: -4.90, -1.41 and -1.01). 26b-5p, 7-5p and 152-3p were downregulated in LMS cells (FR: -1.17, -1.17 and -13.49, respectively). In silico analysis showed that the insulin receptor (INSR) and insulin receptor substrate 1 (IRS1) are target genes to the evaluated microRNAs (INSR: 26b-5p, 195-5p, 15b-5p; and IRS1: 7-5p, 148a-3p, 96-5p, 152-3p). Expression of INSR and IRS1 were evaluated in cell lines and showed that both genes were slightly more expressed in LMS (FR of LM cell line: INSR: 1.00, IRS1: 1.00; FR of LMS cell line: INSR: 1.48 and IRS1: 1.02). The results showed a possible mechanism control of two relevant genes in LM and LMS biology, mediated by miRNAs.

Conclusions

Our data have shown that miR-26b-5p has opposite profiles in the LM and LMS cell lines. MiRNA-mediated regulation of INSR and ISR1 genes may play a key role in understanding the molecular aspects of these tumors.

Gynecological oncology

Small-cell neuroendocrine carcinoma of the endometrium: A case report and literature review

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Objective

The small-cell neuroendocrine carcinoma of the endometrium (SCNEC) is a rare disease, that accounts for 0.8% of the endometrial cancers. Our knowledge about this tumor is based in a few case series and case reports. We present a case of a 62 years-old woman who was diagnosed with SCNEC and relevant literature review.

Patient

A 62 years-old Caucasian female, nullipara, presented with postmenopausal vaginal bleeding. The pre-operative imaging showed an intra-uterine pelvic mass (9x7cm) without any presence of enlarged lymph nodes, ascitic fluid or metastatic tumour. The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy and the histology report revealed a stage IB pure small-cell carcinoma with positive neuroendocrine immunohistochemical features (Chromogranin, Synaptophysin). Following the diagnosis, the patient underwent adjuvant chemotherapy (Cisplatin, Etoposide), radiotherapy and brachytherapy.

Methods

A search conducted by our group in the Pubmed and Google Scholar produced 38 articles (case series or case reports). We included 127 cases in our review and we studied them by fitting them to the following subcategories: age, symptoms, pure/mixed, stage, metastatic location, treatment, recurrence, follow up, and uptaking of staining with chromogranin, synaptophysin, Leu 7, Neuron-specific enolase.

Main outcome measures

From the 128 cases, the mean age of the patients was 60 years old (range 23 to 87), the main presenting symptom was vaginal bleeding, and the patients' staging according to FIGO with stage I 35%, II 4%, III 26%, and IV 32% of the cases. The mean survival time for the stage IV patients was 14.7 months, with 93% dying from disease. In contrast, 77% of stage I patients were free of disease (mean follow up 34 months) and only 11% of them died from the disease (all had mixed type of SCNEC, with a mean survival of 37 months). The majority patients were treated with surgery plus adjuvant therapy (chemotherapy and radiotherapy).

Conclusion

SCNEC is an aggressive cancer, that has worse prognosis than adenocarcinoma. Most of the patients are diagnosed in advanced stages (III, IV). The mixed type seems to be more common in the advanced stages (68%), and worsens the prognosis when diagnosed in stages I and II.

Gynecological oncology

Application of 3d-tumor spheroids in drug discovery

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Introduction

At present, various models are used in experimental oncology, including spontaneous, transplanted, and induced tumors of animals, human tumors transplanted to animals, various cultures of human and animal tumor cells, as well as molecular genetic models. In these latter days special importance is played to *in vitro* models based on cell cultures, including multicellular tumor spheroids (MTS) because of the tightening of the requirements for animal experiments. MTS are artificially produced small solid tumors, which are a three-dimensional (3D) model consisting of cancer cells received by taking a biopsy from a cancer patient. Three-dimensional cultures of tumor cells overcome the limitations associated with such basic characteristics as volume gradients, growth factors, and metabolites and the presence of necrotic, hypoxic, resting, and proliferating cells. The aim was to prove the advantage of the 3D model over the 2D model in order to further integrate the *in vitro* model of tumor spheroids into the design of anticancer drugs and to use primary tumor cells in drug screening studies for the implementation of personalized cancer treatment.

Materials and Methods

In the study, multicellular spheroids generated from a suspension of isolated cells of the immortalized adenocarcinoma cell line MCF-7 of human mammary gland were obtained in the serum. Microcapsules with MTS were incubated in 24-well plates with Methotrexate for 48 hours. The control group was presented by the monolayer MCF-7 culture (100,000 cells per well). Quantitative evaluation of the surviving cells was carried out with trypan blue dye in a Fuchs-Rosenthal counting chamber.

Results

The survival rate of viable cells in the control group was 2 times less than in MTS with a Methotrexate concentration of 100 nM. Evaluation of the cytotoxic effect of Methotrexate, based on the size of MTS was also made. When Methotrexate concentration of 100 nM, the number of living cells was 65 and 88% for spheroids with size of 150 and 300 μm, respectively, while in the control group this value was only 35%.

Conclusion

Compared to monolayer cultures, cancer cells in three-dimensional spheroid cultures demonstrate greater resistance to cytotoxic drugs, with the cytotoxic effect of Methotrexate decreasing while MTS size increasing. In this regard, three-dimensional tumor models are a valuable “tool” for cancer research in the context of drug discovery.

Gynecological oncology

Blocking 17ß-hydroxysteroid dehydrogenase type 1 in an estrogen-dependent orthotopic mouse model of endometrial cancer

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Context
Endometrial cancer (EC) is the most common gynaecological malignancy in the Western society. Over 80% of EC cases are estrogen dependent. Type 1 17β-hydroxysteroid dehydrogenase (17β-HSD-1), responsible for generating active 17β-estradiol (E2) from low-active estrone (E1), is over-expressed in EC. Thus, implicating an increased intra-tumoural generation of E2 in this estrogen-dependent condition.

Objective
Explore the potential therapeutic effect of inhibiting E2 generation in a novel estrogen-dependent orthotopic mouse model of EC.

Methods
Tumours were induced in one uterine horn of athymic nude mice by intra-uterine injection of the human endometrial adenocarcinoma Ishikawa cell line, modified to express the luciferase gene, and 17β-HSD-1 in levels comparable to humans. After tumour engraftment, mice were ovariectomized and controlled estrogen exposure was achieved using subcutaneous MedRod implants that released either E1 or placebo. A subgroup of both E1 and placebo supplemented mice received a daily gavage of the 17β-HSD-1 inhibitor (FP4643). Tumour growth was non-invasively assessed by bioluminescence imaging (BLI). At the experimental endpoint, primary tumours were dissected and weighed. Metastatic spread was evaluated by post-mortem ex-vivo BLI and histological examination. Subsequently, LC-MS was used to profile steroids (E2 and E1) locally (tumour) and systemically (blood).

Results
BLI data showed that mice receiving FP4643 exhibited significantly smaller tumours as compared with mice receiving E1 alone. In line with the BLI data, measurement of tumour wet-weight showed a reduced tumour weight by 40% after FP4643 treatment. Metastatic spread was assessed by ex-vivo BLI and histologically confirmed by H&E-staining. Local and systemic steroid-profiles obtained by LC-MS indicated a reduction in E2 formation upon treatment with FP4643 as compared with untreated mice.

Conclusion
In a mouse-model mimicking human EC, 17β-HSD-1 inhibition significantly reduced tumour growth as compared with untreated mice. These findings are in line with our previous studies investigating the efficacy of FP4643 in-vitro, ex-vivo and in-vivo using the chorion-allantoic membrane model. Our findings open the road for further preclinical and clinical investigations.

Gynecological oncology

Effects of estrogen on the proliferation and nude mouse tumorigenicity of endometrial carcinoma cells by mediating the expression of HOTAIR

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Context
Endometrial carcinoma (EC) is one of the most lethal gynecologic cancers, of which the incidence has increased worldwide in recent years. Extensive studies have shown that long-term effects of high estrogen without progestin antagonists can increase the risk of EC. The overexpression of lncRNA HOTAIR has been confirmed to be closely related to the malignant biological behaviors advances of various tumors.

Objective
To investigate the effect of estrogen on the proliferation and nude mouse tumorigenicity of EC cells by mediating the expression of HOTAIR.

Methods
1. Lentivirus-mediated interference of HOTAIR expression shHOTAIR was constructed and transfected into Ishikawa cells, the expression of HOTAIR was detected by qRT-PCR; Four groups were set up: Control group (Ishikawa cells), E2 group (E2+Ishikawa cells), E2+shNC group (E2+shNC cells) and E2+shHOTAIR group (E2+shHOTAIR cells). QRT-PCR was used to detect the expression of HOTAIR in the four groups.
2. The xenograft tumor model of nude mice treated with E2 and four groups Ishikawa cells of different expression of HOTAIR was constructed. The tumor formation time, the tumor formation rate and the growth curve of the xenograft tumor were recorded. The xenograft tumor was removed, whose volume and weight were measured. The pathological examination of the xenograft tumor was performed.

Results
1. The stable transfected cell lines with lentivirus-mediated interference of HOTAIR expression shHOTAIR and negative control shNC were successfully constructed, and the expression of HOTAIR was effectively inhibited ($P<0.001$); The relative expression of HOTAIR in E2 group was significantly higher than Control group ($P<0.001$), and E2+shHOTAIR group was significantly lower than E2+shNC group ($P<0.001$).
2. The comparison of tumorigenic ability was as follows: E2 group⇒Control group⇒E2+shNC group⇒E2+shHOTAIR group; The final volume ($P<0.001$) and final weight ($P<0.001$) of the xenograft tumor in E2 group were significantly higher than those in Control group, and the final volume ($P<0.01$) and final weight ($P<0.001$) in E2+shHOTAIR group were significantly lower than those in E2+shNC group; The HE staining of the xenograft tumor was consistent with the pathological characteristics of EC cells.

Conclusion
Estrogen promotes the proliferation and nude mouse tumorigenicity of EC cells by up-regulating the expression of HOTAIR, which is expected to provide a new target for the treatment of EC.

Gynecological oncology

Altered profile of E1-S transporters in endometrial cancer: lower protein levels of ABCG2 and OSTb and up-regulation of SLCO1B3 expression

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Context

Endometrial cancer (EC) is an estrogen-dependent disease. Locally, estrogens can be formed from steroid precursor estrone-sulfate (E1-S) after cellular uptake by organic anion-transporting polypeptides (OATP) or organic anion transporters (OAT). Efflux of E1-S is enabled by ATP Binding Cassette transporters (ABC) and organic solute transporter (OST) αb. Currently, 19 proteins are known to transport E1-S but their roles in EC have not yet been examined.

Objective

We analyzed the levels of E1-S transporters in model EC cell lines, Ishikawa and HEC-1-A, control cell line HIEEC, and in paired samples of EC and adjacent control tissue, examined E1-S uptake and metabolism and assessed association between transporters and histopathological and clinical data.

Methods

The expression of 'transporter genes' was evaluated using qPCR and the presence of corresponding proteins was analyzed using imunocytochemistry or imunohistochemistry.

Results

In EC cell lines 14 genes that encode for E1-S transporters were significantly differentially expressed. The highest difference in expression was seen for SLCO1B3 (28930.7-fold up-regulation) and ABCG2 (30.2-fold down-regulation) in model of post-menopausal EC, HEC-1-A, compared to control cell line HIEEC. Imunocytochemistry supported these results and revealed significantly higher levels of E1-S uptake transporter OATP1B3 (SLCO1B3) (6.3-fold) in HEC-1-A compared to pre-menopausal cell line, Ishikawa and low concentrations of E1-S efflux transporter ABCG2 in both EC cell lines. Additionally, increased E1-S metabolism and different E1-S transport profiles were observed in HEC-1-A versus Ishikawa.

In EC tissue statistically significant changes in expression were seen for ABCG2 and SLC51B which were down-regulated (3.2-fold and 2.1-fold, respectively) and ABCC1 which was up-regulated (1.6-fold) in EC compared to adjacent control tissue. Stratification of patients according to the histopathological data revealed 15.6-fold up-regulation of SLCO1B3 in patients without lymphovascular invasion. Tumor grade had effects on expression of SLC51B, with lower levels seen in high grade cancers. Immunohistochemistry revealed significantly lower levels of two efflux transporters ABCG2 and OSTb (SLC51B) and one uptake transporter OATP1B3 (SLCO1B3) in EC compared to control tissue.

Conclusions

Our results confirm the importance of E1-S transporters in pathophysiology of EC and highlight the possible significance of ABCG2, OSTb and OATP1B3.

Steroids and receptors

Immunodetection and quantification of enzymatic markers in theca cells: the early process of ovarian steroidogenesis in human ovary

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Context

The association between theca cells (TCs) and granulosa cells is pivotal to steroid biosynthesis in the ovary, but most data on canonical mechanisms of follicle steroidogenesis come from animal models. Indeed, the specificity of human steroidogenesis has not yet been documented in the ovary. Elucidating the cascade of events in human ovarian tissue would advance TC differentiation research, facilitating development of a transplantable engineered ovary.

Objective

The aim of the present study was to assess expression levels and corresponding amounts of luteinizing hormone/choriogonadotropin receptor (LH/CG-R), perilipin-2 and enzymes involved in the steroidogenesis of TCs based on follicle stage.

Methods

Human ovarian secondary follicles, small and large antral follicles, and corpora lutea (CL) were investigated. The expression intensity of each protein involved in steroidogenesis and their surface area were studied using Image J software.

Patient(s)

Nine patients aged 35-43 years provided ovarian tissue biopsies for analysis.

Results

Proteins involved in steroid biosynthesis exhibit intensifying expression patterns during follicle development. Indeed, LH/CG-R, 3-beta-HSD I and 3-beta-HSD II staining were increasingly observed throughout the ovarian cortex and medulla. LH/CG-R showed focal expression with cytoplasmic and nuclear staining in ovarian stroma, while 3-beta-HSD I and 3-beta-HSD II were expressed mostly in the cytoplasm and sometimes in the nucleus of ovarian stromal cells. 3-beta-HSD I showed the highest expression throughout stromal cells. On the other hand, perilipin-2, CYP11A1 and steroidogenic acute regulatory protein (StAR) were not always detected in secondary follicles.

Conclusions

This is the first time that human ovarian tissue has been used to localize and quantify expression of key steroidogenic proteins. These data may shed new light on pathological conditions of the human ovary, like androgen-secreting tumors and other disorders associated with ovarian TCs in women with polycystic ovary syndrome.

Key words

Enzymes, immunostaining, ovarian follicles, protein expression, steroid biosynthesis

Steroids and receptors

Is there a correlation between progesterone values and histological endometrial parameters?

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We have designed a model for patients with two or more failed cycles of frozen embryo transfer with hormonal treatment and a test for progesterone in the blood on day 4 and a biopsy of the endometrium on day 5 with the transfer of unfrozen embryos at the blastocyst stage. We have called this a pilot cycle
The study is carried out with two different groups in the luteal phase:
Group 1: patients treated with 200 mg of natural micronized progesterone every 8 hours
Group 2: patients treated with 200 mg of natural micronized progesterone every 8 hours and 25 mg per day of subcutaneous progesterone.
The results will be expressed on the basis of different histological parameters and will be correlated by using clinical and laboratory variables.

Steroids and receptors

Value of progesterone in cycles of transfers of frozen blastocyst

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We have conducted a study on cycles of frozen embryo transfer in blastocyst stage.
Blood progesterone was measured on day +4 hormone replacement in two patient groups.
We have performed the analysis in two groups of patients: Group 1 patients with hormonal supplementation based on 200 mgr of micronized natural progesterone. if the value was less than 10.5 ngr / ml in a subsequent cycle, 25 mgr of progesterone was added subcutaneous what would group 2 be.
The value of the determination will be compared in this subsequent cycle.
The objective is to determine, correlating the pregnancy and abortion rate results, if the latter option improves the results.

Steroids and receptors

The peripartum period and differences of steroid hormones levels caused by fetal sex and delivery type

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Context

During pregnancy, from implantation to childbirth, progesterone, estrogens, androgens and glucocorticoids all play important roles. Their synthesis and metabolism are the result of complex metabolic pathways encompassing activities in the fetus, placenta, and mother. Progesterone, estrogens, androgens and glucocorticoids all play important roles during pregnancy, from implantation to delivery.

Objective

Focusing on selected steroid hormones in the peripartum period, we defined reference ranges measured using LS-MS/MS, and assessed relationships with maternal age, pregnancy weight gain, delivery type, and fetal sex.

Methods

Samples were taken from 142 healthy women with physiological gravidity at the 37th week, during the first period of labor, and from newborn mixed cord blood. The local ethical committee approved the study.

Results

We found higher cortisol and 17-OH-pregnenolone plasma levels in mothers at the 37th week that carried male fetuses (p=0.03), but no significant differences in any studied hormones in newborns of different sex. Neither maternal age, weight gain nor newborn birth weight had any relationships to any of the studied hormones. However, there were differences depending on vaginal versus planned cesarean section deliveries. In women carrying a male fetus we found significantly higher levels of 17-OH-pregnenolone, progesterone, cortisol, corticosterone and significantly lower levels of estradiol in those undergoing spontaneous vaginal delivery. However, we found no significant differences in the cord blood of newborn males from either delivery type. We established reference ranges for our analysis methods, which should be useful for further studies as well as in standard clinical practice.

Conclusions

We found changes in steroid levels in women associated with delivery type, and demonstrated the necessity to analyze steroid changes taking the fetal sex into consideration, even though no differences were found in newborns at birth. We also calculated reference ranges for our analysis methods, which should be useful both in further studies and in routine clinical practice.

Acknowledgments

The study was supported by the project MH CZ - DRO (Institute of Endocrinology - EÚ, 00023761), and by the grant MH CR 17-30528 A from the Czech Health Research Council.

Steroids and receptors

Comparison of estradiol and estetrol on estrogen receptor alpha signaling

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Context
Estetrol (E4) is a natural estrogen produced by the human fetal liver during pregnancy. However, the physiological roles of E4 during pregnancy remain unknown. Several evidences highlight that E4 is a promising compound for clinical applications in estrogen-sensitive tissues, since it elicits a high binding specificity for both estrogen receptors, ERalpha and ERbeta. E4 treatments in rodents and women revealed that it shares with Estradiol (E2) and Estriol (E3) several estrogen-like effects on numerous tissues such as brain preventing hot flushes, endothelium protecting from atheroma, bone preventing osteoporosis or vaginal epithelium avoiding vaginal dryness. E4 has also characteristics distinctive from other estrogens, which makes it an appropriate compound to be used for menopause hormone treatment (MHT) or combined oral contraceptive (COC) in women. Nevertheless, it remains essential to document the molecular and cellular mode of action of E4 and to compare it to E2, especially regarding its impact on ERalpha signaling that relays most of the physiological effects of estrogens.

Objective
The aim of this study was to compare E4 and E2 on several steps of ERalpha signaling.

Results
The ERalpha signaling relies on two main pathways: 1) the genomic/nuclear pathway that is associated to the direct ability of ERalpha to bind to specific DNA sites to modulate the expression of target genes, 2) the rapid/non-genomic/membrane-initiated steroid signaling (MISS) that is related to the activation of the membrane form of ERalpha. In this study, we compared how E2 and E4 modulate these two pathways. To specifically study the genomic pathway we evaluated the ability of E2 and E4 to induce the phosphorylation of ERalpha, one of the first step of ERalpha activation, to bind to DNA estrogen responsive element (ERE) and to induce the expression of genes (PR, pS2) specifically related to the genomic pathway. The activation of the MISS pathway was studied by measuring the interaction between ERα and Src, the initiating step of the MISS effects. Induction of specific genes of the MISS pathway (PMAIP1, TSKU, HSPB8) were also evaluated. Finally, we compared the broad transcriptomic impact of E2 and E4.

Conclusions
This study provides a comprehensive comparison of the impact of E4 and E2 on ERalpha signaling. This allows a better understanding of the specificity of E4 action on several estrogen-sensitive tissues.

Steroids and receptors

Saw palmetto as a novel therapy for acne vulgaris associated with excess level of androgens

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Context
Acne vulgaris is a common chronic skin disease, which has a substantial impact on a patient's quality of life. Androgen excess is a frequent cause of acne vulgaris. Nonsteroidal antiandrogenic drug flutamide is widely used in the clinical practice of acne and hirsutism treatment. Serenoa repens (saw palmetto) is a plant-derived drug that has an inhibitory effect on the enzyme 5alpha reductase (5aR) and may be effective in patients with peripheral hyperandrogenism and high levels of dehydrotestosterone (DHT).

Objective
The goal of this study was to assess the efficacy of flutamide as monotherapy and in association with saw palmetto in women with acne vulgaris and excess of androgens.

Methods
The women with acne vulgaris >18 years old were divided into two groups randomly. In group 1 (n=28) patients with acne and hyperandrogenism received a low dose flutamide (250 mg/day) in association with extract saw palmetto (320 mg/day). Group 2 (n=24) received monotherapy flutamide (250 mg/day). The time before the onset of clinical effect on acne therapy was estimated in two groups. The assessment of adverse effects as well as blood biochemistry with hepatic enzymes was carried out. The DHT level was estimated before treatment and after 3 months. Photos were taken for all patients before and after treatment.

Results
The average follow-up period was 3 months. In group 1 the good clinical effect occurred in 93% patients in 4.2 weeks (95% CI 3.7-4.7, P=0.003). In group 2 it was in 88% patients in 6.7 weeks (95% CI 6.2-7.1, P=0.09). The clinical effect was observed not only for acne vulgaris, but also for hirsutism and androgenetic alopecia. 60% of all patients were under 25 years old. It was found a significant decrease in DHT level in one-third of patients (28.6%) of group 1. Dryness of the skin was observed 2 times more often in group 1 (25%) than in group 2 (12.5%). Elevated liver enzymes were equally observed in 2 groups in 3 (10%) and 3 (12.5%) patients, respectively. There was no clinical effect in 1 (3.6%) vs. 2 (8.3%) women in two groups.

Conclusion
A low dose flutamide in association with saw palmetto is effective for the clinical improvement of androgen-dependent dermopathy. Saw palmetto seems to be an additional safe and effective dietary supplement for acne vulgaris treatment in women. Further studies are needed to evaluate this combination.

Steroids and receptors

Identification of PGRMC1 as a novel oncogene for human cancers and its involvement in metabolic activities

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Context
Progesterone-receptor membrane component 1 (PGRMC1/Sigma-2 receptor) is a haem-containing protein that interacts with epidermal growth factor receptor (EGFR) and cytochromes P450 to regulate cancer proliferation and chemoresistance. Although it is over-expressed in many different types of human cancers, systematic analysis of the oncogenic role of PGRMC1 has not been reported for any cancer. Recent studies revealed that PGRMC1 dramatically elevated in head and neck squamous cell carcinoma and oral cancer (Hampton et al., 2015). However, the biological roles of PGRMC1 in human head and neck cancer have not been systematically analyzed, and additional researches are merited. This study provides insights into the oncogenic functional significance of PGRMC1 in human cancers.

Objective
In order to gain a better understanding of the significance of PRGMC1 in head and neck carcinogenesis.

Methods
Here we analyzed the genomics, transcriptomics, and clinical data of 498 head-neck squamous cell carcinoma (HNSC) samples from the clinically annotated genomic database, The Cancer Genome Atlas (TCGA). The Cox regression was performed to calculate the hazard ratio (HR) of PGRMC1 expression as a prognosis feature for overall survival (OS).

Results
Our results demonstrated that PGRMC1 over-expression served as a predictor for worse OS (HR=1.95, P=0.0005) in head and neck cancer, and many other cancer types (breast cancer, acute myelocytic leukemia, and sarcoma). Besides, the over-expression of PGRMC1 was strongly correlated with metabolic process activity as well as cancer metastasis features, but negatively correlated with immunological reaction features in human head-neck squamous cell carcinoma patient's cohort.

Conclusion
Our data demonstrate that PGRMC1 plays an unfavorable prognosis marker role in head and neck cancer, breast cancer, acute myelocytic leukemia, and sarcoma. These findings uncover the potential of PGRMC1 as an oncogene, prognosis marker and therapeutic target for human cancer patients who over-express this gene.

Steroids and receptors

Serum levels of Insulin-like Growth Factor-I and its binding protein 1 in relation to body composition and physical performance in female Olympic athletes

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Context
Anabolic hormones may affect body composition and physical performance in athletes. However, very little is known about the role of insulin-like growth factor-I (IGF-I) for body composition and physical performance in female elite athletes.

Objective
To study serum levels of IGF-I, age-adjusted IGFSD and its binding protein IGFBP-1 in female Olympic athletes of different sport categories compared to untrained controls in relation to body composition and physical performance in the athletes.

Methods
In this cross-sectional study, Swedish female Olympic athletes (n=103) and age- and BMI- matched untrained controls (n=113) were included. Athletes were divided into power, endurance and technical disciplines. Serum IGF-I and IGFBP-I were measured by radioimmunoassay and IGFSD calculated using a logarithmic equation. Body composition was determined by dual- energy X-ray absorptiometry. Athletes performed standardised physical performance tests.

Results
Athletes demonstrated higher levels of IGF-I ($p < 0.05$), IGFSD ($p < 0.05$) and IGFBP-1 ($p < 0.01$) than controls. Athletes in the power group had the highest IGF-I levels and higher IGFSD compared to athletes in the endurance ($p < 0.05$) and technical ($p < 0.01$) groups. Weak correlations were found between IGF-I parameters and lean body mass in the whole population. In the athletes, IGF-I, but not IGFSD correlated with squat jump.

Conclusions
Serum levels of IGF-I, IGFSD and IGFBP-1 are higher among female Olympic athletes than age- and BMI-matched controls and differ between sport categories. Our results suggest that endogenous IGF-I may be of importance for power performance and elite athletes participating in strength sports. However, further studies are warranted to elucidate underlying mechanisms and potential causality behind the associations.

Puberty and adolescent gynecology

The gynecologist's role in treatment of patients with disorders of sex development

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National Children's Specialised Hospital "Ohmatdyt"

Objective

DSD are congenital defects where chromosomal, gonadal and anatomical sexes do not align. Optimal treatment includes:
• Choice of gender (not always the gonadal sex)
• Gender choice factors include fertility potential; need/possibility to form external sex organs via plastic; gonad malignancy risk.
• Phenotype/gender correspondence helps in raising a child.
• Gender choice, surgical correction and long-term treatment done at center with a multi-disciplinary team;

Main Outcomes

The NCCH"OHMATDYT" team includes an endocrinologist, geneticist, gynecologist, psychologist, urologist, neonatologist and a social worker. After examination, the team gives gender choice and treatment recommendations for parent (and older child) decision-making.
In our team the gynecologist:
• Is present at the start of examination to discuss future results;
• Evaluates sexual and reproductive function, surgery prospects, explains the diagnosis,
• Initiates and oversees long term sex hormone therapy.
We analyzed treatment of 75 DSD patients in 2004 – 2019 at "OHMATDYT": DSD 46 XY -41, DSD chromosomal genesis -11, DSD 46 XX- 23
Average patient age at surgical intervention was 14.3 years.
All patients were socialized by name as females.
There is gonad malignance risk where Y chromosome is present, especially with mosaic cariotype and gonad-in-abdomen. Treatment is by well timed mini-invasive surgery - gonadectomy, followed by hormone replacement therapy; upon feminized appearance, psychological state and social adaptation are evaluated.
When female gender is chosen and virilization required, operations follow for normal localization of vaginal entrance, separating the vagina from the urinary tract; reduction of clitoral size by cavernous body reduction, maintaining the glans, its enervation, sensitivity and blood supply.
Before surgery, benefit/risk analysis is done (re complications and patient age).
In feminizing plastic of external sex organs in 39 DSD patients, 14 involved only plastic of clitoris; 16 – of urogenital sinus. 10 girls required plastic of both clitoris and urogenital sinus.
Timing of feminizing operations/gonad removal remains controversial.

Conclusions

- DSD treatment is best done by a multi-disciplinary team, combining short-term interventions and long-term observation.
- At DSD, gender choice made based on evaluation by a multi-disciplinary team accounting for surgical and hormonal correction.
- Feminizing plastic and gonad removal are best timely done based on joint caregiver-parent decisions.
- Contemporary plastic in DSD patients choosing female gender improves quality of life
- HRT with estrogen provides feminized appearance and improves the patient's psychological state and social adaptation

Puberty and adolescent gynecology

Surgical treatment of rare genital abnormalities in adolescent girls

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Objective

Congenital abnormalities of genitals in girls - complex problems of child and adolescent gynecology.

Main Outcomes

175 girls with congenital anomalies; 62,85% - complex uterovaginal anomalies. Many require further evaluation, carefully planned surgical treatment and follow up. Hemi-uterus with non-communicative functional horn –is rare, 3,42% of cases. This malformation presents with severe dysmenorrhea from menarche and requires surgery, mainly laparoscopy. Histological samples often show adenomiosis; endometriosis is a concern.

Bicorporeal uterus with hemiobstructed vagina is rarer, 33,14% among patients. We perform plastic of the obstructed vagina wall to provide unimpeded blood flow. Bicorporeal uterus may present with atresia of cervical canal resulting in haematometra and haematocervix, 15,42% of cases. Surgical creation of the cervical canal is difficult with high stricture and inflammatory complications risks.

Completely septate uterus with haematometra at one side, caused by unilateral cervical aplasia is hard to diagnose, with six cases (3,42%) observed. Surgery with removal from the uterus with aplastic cervix was completed and uterine function preserved.

Yet more complex is a single uterus with disrupted menstrual outflow due to atresia of the cervical canal or partial vaginal aplasia (4%). In the first, more favorable case we create an orifice for the cervical canal. In the second case we conduct a two-stage operation: first we create a vagina, laid out (lined) with by oxygenated cellulose (2,28%). After neovagina epithelization we create an external orifice for the cervical canal.

Complete vaginal aplasia combined with cervical aplasia and a functioning uterus is hardest to diagnose and treat. Even after vagina creation, functional cervical canal creation is difficult. Stricture and septic complications risks are very high.

Complete vagina aplasia with a functioning rudimentary cavity is very rare (2,85%) - only cavity removal is done.

Selecting a treatment strategy and conducting surgical intervention are very complicated in girls with anorectal atresia, often with accompanying defects in spine, kidneys, and internal/external sex organs development. Such girls have undergone 3 or 4 phase surgeries for anorectal atresia prior to puberty, when such anomalies may present. Among 6 girls (3,42%) examined and treated, 3 had pre-pubertal genital inflammation requiring long antibacterial therapy, pyosalpinx removal, abscess opening/drainage.

Conclusions

The treatment of patients with rare genital anomalies requires an experienced multi-disciplinary team; Endometriosis prevention is a must; proper evaluation and clear understanding of the anomaly point to proper surgical intervention options.

Contraception

Contraceptive efficacy and bleeding pattern of a new COC containing estetrol 15 mg and drospirenone 3 mg - phase 3 trial results

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Context

Estetrol (E4) is a naturally occurring estrogen that demonstrates unique tissue specific actions. These properties make E4 an ideal candidate for use as a contraceptive.

Objective

We assessed the contraceptive efficacy and safety of E4 15 mg combined with drospirenone (DRSP) 3mg in a 24/4-day regimen during use for up to 13 consecutive cycles (1 year).

Methods

Multicentre, open-label, phase 3 trial conducted in 69 centres across Europe and Russia.

Patients

We enrolled healthy women age 18-50 years with regular cycles and BMI ≤35.0 kg/m^2.

Interventions

Subjects used study drug daily and recorded pill intake, other contraceptive method use, and bleeding/spotting episodes in a daily diary. Follow-up evaluations were scheduled after 2, 4, 7, 10, and 13 cycles.

Main outcome measures

Primary efficacy endpoint was on-treatment pregnancy in women 18-35 years old, measured by the Pearl Index (PI) in at-risk cycles (no other contraceptive use). Secondary outcomes included bleeding patterns and safety.

Results

Overall, 1,343 subjects provided 14,759 at-risk cycles, Five on-treatment pregnancies occurred (PI 0.44 [95% CI 0.14–1.03]) of which 2 were method failures (method failure PI 0.26 [95% CI 0.05-0.77]). Withdrawal bleeding occurred in >92% of cycles, generally from Day 26 to Day 3 of the next cycle. Over the first 12 cycles, median duration of scheduled bleeding/spotting was 4-5 days, lasting from Day 26 to Day 3 of the next cycle. Two days of withdrawal bleeding/spotting episodes was only spotting. Unscheduled bleeding and/or spotting episodes decreased from 23.5% in Cycle 1 to 12.8% at Cycle 11. Less than 20% of women experienced any unscheduled bleeding/spotting episodes and <1.5% of subjects experienced only unscheduled bleeding /spotting episodes. The median number of unscheduled bleeding days by cycle was 0, while the median number of unscheduled spotting days by cycle was 2-3 days. No relevant changes were observed in any physical examinations or laboratory parameters, including haematology, biochemistry, or lipid profile. The most common treatment-related adverse events were metrorrhagia (5.0%), vaginal haemorrhage (4.3%), acne (3.8%), and headache (2.8%); discontinuation rate for these events was 9.1%.

Conclusion

E4 15 mg/DRSP 3 mg shows high contraceptive efficacy and excellent cycle control. The treatment is well-tolerated without evidence of unexpected safety concerns typical for COCs.

Contraception

Six-year efficacy and safety of the levonorgestrel 52 mg intrauterine system

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Context

The levonorgestrel (LNG) 52mg contraceptive intrauterine system (IUS) is approved for 5 years duration for contraception and is under investigation in an ongoing U.S. multicenter Phase 3, pivotal trial for up to ten years of use.

Objective

To assess the 6-year contraceptive efficacy and extended safety of the LNG 52 mg IUS.

Methods

After IUS placement, we followed 1,568 women aged 16-35 years and 146 women aged 36-45 years, assessing pregnancy rates through six years and safety outcomes in all women regardless of duration of use.

Patients

1,600 women aged 16-45 years with 151 participants aged 36-45 years undergoing safety evaluation only.

Intervention

IUS placement.

Results

The 16-35 year-old subjects included 986 (57.5%) nulliparous and 433 (25.3%) obese women. To date, more than 375 women have completed 6 years of use; more than 125 have completed 8 years. Nine pregnancies occurred over 6 years including two in year 1, four in year 2, one each in years 3-5, and none in year 6. Six (67%) pregnancies were ectopic. The cumulative life-table pregnancy rate through year 6 was.87 (95% CI.44-1.70). Two perforations following IUS placement were diagnosed within the first year and none since. Expulsion occurred in 68 (4.0%) participants, most (50 [73.5%]) during the first year with 2 per year in years 6 and 7. Pelvic infection was diagnosed in 15 (.9%) women, most (11 [73.3%]) occurring after 6 or more months of use. Only 40 (2.3%) women discontinued due to bleeding complaints, primarily (n=30 [75.0%]) in the first 2 years.

Conclusions

The LNG 52 mg IUS is highly effective over six years of use and has an excellent extended safety profile. The most frequent adverse events, expulsions and bleeding complaints, were uncommon and occurred mostly during the first years of use.

Contraception

Combination of use of dienogest with LNG IUD Mirena

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Objective

Currently the intrauterine hormone-releasing system Mirena is widely used for the purpose of treatment of metrorrhagias, endometrial hyperplasias and adenomyosis. In recent years, duet introduction of 3D ultrasound into clinical practice, the research, aimed at identification of IUD expulsion risk factors came forward.

Methods

In previous works we established, that expulsion risk factors, apart from uterine cavity deformations, are extended area of uterine cavity (S) >9 cm^2, associated with increase of distance between tubal angles (L) >4,5 cm. However, in certain cohort of patients, application of Mirena, due to a range of causes, including compliance in case of necessity of long-term application, is preferable. Another widely used medication for treatment of metrorrhagias, endometrial hyperplasias and adenomyosis is dienogest (Visanne).

Main outcome measures

25 patients with previous expulsions of Mirena with uterine cavity area >9 cm^2 (in the average12,46±1,96 cm^2), distance between tubal angles > 4,5 cm (in the average4,98±0,42 cm), dienogest was prescribed 2mg daily during 6 months, after which patients underwent 3D ultrasound again.

Results

Ultrasound transformation of myometrium and uterine cavity parameters after 6 months of Visanne administration in 18 (72%) patients was expressed by reduction of the uterine cavity area in the average down to 7,87±0,61cm^2 and reduction of distance between tubal angles in the average down to 4,04±0,10 cm.

These patients had Mirena introduced again. During 3, 6 and 12 months of observation after its introduction no cases of Mirena expulsion were identified.

Conclusions

According to data received, the combined sequential application of dienogest and Mirena reduces probability of IUD expulsion.

Pregnancy: placenta and foetal membranes, thyroid

Radiant flow and 3D HD power Doppler flow ultrasound in detection of vellamentous insertion of umbilical cord

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Objectives

The aim of our study was to analyse the application of Radiant Color Doppler Flow and 3D HD Power Doppler Flow in confirmation of vellamentous insertion of umbilical cord.

Methods

In a two year period we examined 5120 patients and analysed placental insertion and also insertion of umbilical cord. Examinations were performed on General Electric Voluson E10 with transabdominal probe RMC6 and General Electric Voluson E8 with transabdominal probe RAB6. Umbilical cord insertion was checked in color Doppler mode with Radiant flow. When suspicious finding was detected, 3DHD power Doppler flow was applied in order to confirm vellamentous umbilical cord insertion. 3D volume was obtained in power Doppler mode, High2 resolution with sweep angle of 45 degrees. Futher analysis was perforemed in Gloss Body mode with color and monochrome reconstruction of umbilical vessels position.

Results

In the studied period we detected 5 patients with vellamentous insertion of umbilical cord. Vellamentous insertion was detected in two patients with singleton pregnancy in second trimester. They both had vasa praevia confirmed with 3D HD flow with vessels overlying internal cervical orifice and isthmic part of the uterus. Placental insertion was on the anterior wall and umbilical cord insertion on posterior wall of the uterus. Three patients had twin pregnancy with septal vellamentous insertion. All patients were followed up until delivery. Patients with vellamentous insertion were delivered by caesarean section and umbilical cord insertion confirmed after extraction of the placenta.

Conclusion

Vellamentous umbilical cord insertion can be screened by Radiant color flow and definite diagnosis can be confirmed in 3DHD power Doppler mode. In order to prevent obstetrical complications pregnancies with vellamentous insertion were terminated by caesarean section.

Pregnancy: placenta and foetal membranes, thyroid

Iodine supplementation in pregnancy

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Iodine can be absorbed as iodide and plays a major role in the synthesis of thyroid hormones. The iodide is transported into the follicular cell with the sodium-iodide symporter (NIS) to be attached to the tyrosine molecule thereafter forming thyroxine (T4) with the thyroid peroxidase enzyme. The T4 is partially deiodinated withtin the thyroid gland to thyronine (T3) and the iodine is reused. The thyroid hormones are further deoidinated in the target organs which can either result in the activation of T4 to T3 or inactivation to reverse T3 (rT3). The iodide is partially recycled by the thyroid gland, mostly excreted by urine and stool. It is important to note that the iodide content of the supplemented levothyroxin (LT4) may be reused likewise.
Hungary is considered to be an iodine deficient area, the iodine content of drinking water is mostly at or below 30μg/l which means a daily supply of 50-60μg. Iodised salt is readily available, most salts contain 15μg/g iodide. The average salt consumption for males and females is 16g and 11g respectively, resulting in a daily 150μg iodide supplementation. All the WHO, ATA, ETA Guidelines suggest a daily intake of 250μg iodine during pregnancy and lactation, this can be achieved by a daily supplement of approx. 150μg of iodine, which should be started during the planning of the pregnancy. Doses above 500μg should not be taken.
A marked elevation in total T4 levels can be observed starting from the first weeks and of pregnancy and persisting throughout. Since the fetal thyroid is not fully developed until the 20th gestational week, the placenta provides the fetus with thyroid hormones, mostly T3 and iodine. During the second half of the pregnancy, both the placental iodine absorption and deiodination are elevated producing free iodide for the fetus. The lactating breast has a likewise high NIS and deiodinase activity.
According to the 2017 ATA Guideline iodine supplementatio is not required in pregnant women receiving LT4 supplementation. Besides being unnecessary iodine consumption in hypothyroid patients may have unwanted effects: the Wolff-Chaikoff effect may be more pronounced, onset at smaller iodine doses with a prolonged escape mechanism resulting in TSH elevation. Moreover, excessive iodine supplementation may enhance thyroid autoimmunity and autoimmune thyroid disorder.

Pregnancy: placenta and foetal membranes, thyroid

Placental villous hypermaturation is associated with *in vitro* fertilization

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Context

Accelerated placental maturation is regarded as a sign of vascular malperfusion, and is often interpreted as a compensatory response by the placenta. *In vitro* embryo culture affects placental development.

Objective

Placental manturation was assessed in spontaneous conceived and *in vitro* conception pregnancies.

Design & Methods

Retrospective cohort study on single-center between 2014-2017. For this study preterm placentas of singleton pregnancies between 24 and 36 weeks were considered. Routine placental examinations were retrospectively reviewed.

Results

During the considered period 423 placentas of singleton pregnancies were assessed. 396 placentas were from spontaeous conception and 20 from *in vitro* fertilization. The placental villous hypermaturation was significantly more common among *in vitro* fertilization (15.00%) than in spontaneous conception (4.55%) ($p<0.05$). In addition, cotyledon hyporamification was significantly more common *in vitro* fertilization (10.00%) than in controls (2.02%) ($p<0.05$).

Conclusions

Placental villous hypermaturation and cotyledon hyporamification were significantly associated with *in vitro* fertilization in singleton pregnnacies. This result adds evidence in support to the hypothesis that villous hypermaturation is a compensatory response by the placenta to improve its transport capacity in specific settings such as *in vitro* fertilization.

Steroid hormones and ageing

DHEA restores central and peripheral BDNF levels in female castrated rats

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BDNF is a neuroprotein growth factor involved in development and modulation of the central and peripheral nervous system. Given its maximum concentration in areas such as hippocampus, hypothalamus and parietal and frontal cerebral cortex, BDNF plays an essential role in processes such as memory and learning, through apoptotic stimulation or conversely to neuronal proliferation.
Changes related to sex, age and the hormonal environment induce a different expression of BDNF in brain, emphasizing its role in different cognitive processes. Indeed, the presence of an estrogen response element (ERE) in the BDNF gene further supports this evidence.
In parallel DHEA and its ester DHEAS emerge as the most abundant steroid hormones in the human body. These neurosteroids, acting as modulators of neurotransmitter receptors, thanks to their marked neurotrophism, may be able to protect brain from aging, improving memory, language, mood and sexual behaviour. Physiologically the concentrations of DHEA and DHEAS in humans generally decrease steadily with age, approaching a nadir approximately when many aging diseases become more prevalent.
According to these data, the aim of our experimental study was to detect possible variations in BDNF levels in specific brain areas and in plasma after the administration of different doses of DHEA in female ovariectomized rats.
A total of 60 healthy Wistar rats were used and divided into six groups (N = 10 rats per group). Bilateral ovariectomy was performed, with the only exception of the fertile control group. Oral treatment started 2 weeks after surgery, with E2V (0.05 mg / kg / day) in combination with several doses of DHEA (1, 2 and 5 mg / kg / day). All treatments lasted 14 days, a time proved to be sufficient to determine the changes in the environment of the neuroendocrine rats. As expected, ovariectomy significantly reduced BDNF levels in all tissues examined and in plasma; then after the administration of estradiol, BDNF reached again levels in the range of fertile controls in the frontal and parietal lobes. Administration of DHEA at a dose of 1 mg / kg / day had no effect on the increase in BDNF in all brain areas and in plasma while DHEA 2 mg / kg / day improved the BDNF content in hypothalamus, hippocampus and in frontal and parietal lobe and at the highest dose (5 mg / kg / day) increased BDNF levels also in plasma.
Considering that DHEA represents a precursor of estrogens and androgens, exercising many actions indirectly through ER and AR, its oral supplementation in menopausal women could intervene on the mechanisms of memory, learning and mood by improving the negative symptoms related to this paraphysiological condition. However, the rate of DHEA converted to estrogen/testosterone in different tissues and the presence of enzyme regulators and the effect of the aging process on DHEA require further investigation. For this reason our experimental model lays the foundations for studying a new therapy capable of counteracting the effect of aging related to menopausal hormone decay.

Steroid hormones and ageing

Sex hormones interaction with trabecular bone score and mineral density in men

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The aim of this study was to evaluate the relationship of sex hormones with bone quality and mineral density in men.

Materials and methods

We've examined 72 men aged 40-87 years. Depending on their body mass index (BMI), all the subjects were divided into 2 groups: Group I – 19 men with obesity whose BMI was ≥30 kg/m^2 (mean age 60.3±10.8 years, height – 177.3±5.8 cm, weight – 102.5±7.6 kg, BMI 32.6±1.9 kg/m^2), and Group II – 53 men without obesity and BMI of <30 kg/m^2 (mean age – 60.5±13.5 years, height – 174.6±6.9 cm, weight – 79.2±10.3 kg, BMI – 25.9±2.4 kg/m^2). The BMD of lumbar spine at the site L1-L4 and femoral neck were measured by DXA (Prodigy, GEHC Lunar, Madison, WI, USA). The TBS of L1- L4 was assessed by means of TBS iNsight® software installed on our DXA machine (product of Med-Imaps, Pessac, France). Total testosterone and SHBG were measured in all the subjects using an enzyme immunoassay method. The level of free testosterone was calculated using the ISSAM website calculator.

Results

In general, we found that obese men have a significantly higher BMD at the level of lumbar spine (group I – 1.402±0.232 g/cm^2, group II – 1.203±0.245 g/cm^2, F=9.08, p=0.004) and femoral neck (I group – 1.050±0.141 g/cm^2, group II – 0.925±0.164 g/cm^2, F=8.80, p=0.004) in comparison with men of no obesity. Significant differences between the groups for the TBS were not found. When assessing the hormonal status in men, it was revealed that obese men have a significantly lower total testosterone (group I – 12.55±3.48, group II – 17.64±6.10, F=11.74, p=0.001) and SHBG (group I – 43.03±20.27, group II – 58.15±25.39, F=5.46, p=0.02). However, the probable differences in the levels of free and bioavailable testosterone were not found. The level of SHBG increased with age and there was a probable negative correlation with BMD of femoral neck (r=-0.39; p<0.001). There was no significant correlation between total testosterone and BMD of femoral neck in men with a normal body weight (r=-0.19, p=0.2) and an obesity (r=0.02, p=0.93). Significant association between TBS and sex hormones in men was not revealed.

Conclusions

Men with obesity have a significantly lower total testosterone and SHBG, but their BMD is significantly higher than the one of men with a normal weight.

Steroid hormones and ageing

Hyaluronic acid concentration of diabetic rat vaginal tissue under treatment with 17ß-estradiol

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Objective

this study aims to evaluate the concentration of hyaluronic acid in the extracellular matrix from diabetic rats' vaginas treated with 17b estradiol.

Methods

We used 25 female, adult (3 months old) rats, separated in s groups: GI (n=5) control Sham non ovariectomized; GII (n=5) control Sham non ovariectomized diabetic rats; GIII (n=5) control ovariectomized rats that received propylene glycol; GIV (n=15) ovariectomized diabetic rats that received propylene glycol; GV (n=15) oraviectomized diabetic rats treated with estrogen (17b estradiol, 10ug/Kg, subcutaneous). All animals were treated for 90 consecutive days, then anesthetized and finally had their vaginas removed and processed for biochemical and immunohistochemical analyzes and hyaluronansyntases (HAS 1, 2 and 3) gene expression. It was used the ANOVA One-way test, followed by the Tukey test ($p<0.05$).

Results

The treatment with estrogen increased the hyaluronic acid concentration, the imunohistochemical and gene expression of HAS 1, 2 and 3.

Conclusion

17-beta estradiol stimulate the synthesis of hyaluronic acid in rat vaginal tissue.

Steroid hormones and ageing

Action of hormonal therapy in amyrotrophic lateral sclerosis: a systematic review

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Amyotrophic Lateral Sclerosis (ALS), a fatal disease characterized by muscle and fasciculations weakness and atrophy and decreased reflexes due to upper and lower motor neurons death. It can be present in both sexes (55-65 years), but with predominance in males. However, in female patients, ALS presents its first symptoms when they are already postmenopausal, when then the incidence ratio of the disease is practically equal between the sexes. Which leads to a probable involvement of sex hormones in the development and protection against ALS. The aim of this systematic review, which used the PRISMA consensus and NOS (New Casttle-Ottawa Scale) score, was to evaluate the evidence of the action of hormone therapy in women with ALS. The Medline and Cochrane databases were accessed from March 2019 to June 2019, and only full text articles in Spanish, English and Portuguese languages were included. Only four articles matched our inclusion criteria. Postmenopausal women who used exogenous estrogen did not have the same protective factor as women still under the action of endogenous estrogen in the same age group. There was also no increase in survival of these women.

Steroid hormones and ageing

Effects of estrogen deficiency followed by streptozotocin-induced diabetes in periodontal tissues of female rats

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Objective

Despite both estrogen deficiencyand diabetes have been reported to cause deleterious effects in periodontal tissues, the effects of these conditions combined on periodontium has have not been investigated. Thus, we aimed to investigate the combined effects of ovariectomy followed by streptozotocyn (STZ)-induced diabetes on periodontal tissues of rats.

Materials and methods

Twenty adult rats were ovariectomized (OVX) or SHAM-operated (SHAM). After three weeks, ten rats (five OVX and five SHAM) received a single intraperitoneal injection of STZ (60 mg/kg/body weight) to induce diabetes, whereas the remaining rats received vehicle solution. The groups were then assigned as follows (n = 5): SHAM-vehicle (SHAM), OVX-vehicle (OVX), SHAM + STZ-induced diabetes (SHAM-Di), and OVX + STZ-induced diabetes (OVX-Di). Seven weeks post STZ-diabetes induction, the rats were euthanized. Blood samples was collected for glucose measurements and maxillae were harvested and processed for paraffin-embedding. Sections were stained with hematoxylin & eosin to analysis alveolar bone loss, whereas others sections were subjected to Masson's Trichrome or to the picrosirius-redpolarizarion methods, for collagen fibers evaluation in the lamina propria of the periodontium. Some sections were also subjected to immunohistochemistry for the detections of Runx2, Matrix metallopeptidase 9 (MMP9) and tryptase.

Results

Significant alveolar bone loss was only observed in the OVX-Di group, whereas collagen fibers with irregular organization were more evident in the diabetic groups. However, the lower content of collagen fibers were noticed in the OVX-Di group. MMP9 immunoreactivity was more evident in the lamina propria of diabetic groups, whereas no differences in the number of MMP9-positive osteoclasts on alveolar bone surface were observed among groups. The OVX-Di group showed the lower Runx2 immunoreactivity in the lamina propria, a marker o osteoblast formation, and the higher number of tryptase-positive cells (mast cell marker), in the alveolar bone marrow.

Conclusion

Our results indicate that estrogen depletion, followed by STZ-induced diabetes, promotes deterioration of periodontal tissues that is more evident than both interventions applied alone. Furthermore, our results points to a possible participation of bone derived-mast cells in this process.

Steroid hormones and ageing

Prevalence of sarcopenia with the sarc-f screening scales and its SARC-F+CC and SARC-F+A+BMI versions in Colombian women

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Context
Sarcopenia is the loss of strength and muscle mass. SARC-F [Strength, aid to walk, rise from a chair, climb stairs, falls] has been suggested as a screening test. There are versions to improve the diagnostic capacity: SARC-F-6 or SARC-F + CC, which adds calf circumference and SARC-F-7 or SARC-F + A + BMI, assesses age and body mass index (BMI). There are not enough screening studies on sarcopenia in Latin American women, who have biological, psychological and social conditions that differentiate them from women from other latitudes

Objective
To compare the prevalence of sarcopenia identified with SARC-F, SARC-F + CC (with two cut-off points) and SARC-F + A + BMI.

Methods
Cross-sectional study that is part of the project Quality of Life in Menopause and Colombian Ethnicities (CAVIMEC). EPI-INFO was used for the analysis. The quantitative variables are presented in means and standard deviation and qualitative variables in absolute values, percentage and 95% CI. Anonymous and voluntary study, endorsed by the University of Cartagena. Colombia.

Patients
Women 60-75 years old, black or mestizo race, residents in the Caribbean or in the west of the Republic of Colombia, invited to participate in their own homes.

Intervention
The SARC-F was applied. CC and BMI were measured. Two cutoff points for calf circumference <31 cm and <33 cm were estimated, for BMI ≤21 kg/m2.

Main outcome measures
SARC-F, SARC-F + CC, SARC-F + A + BMI.

Results
700 women, between 60-75 years old, were studied. Average age: 67.0 ± 4.8. 300 (42.8%) of mestizo race and 400 (57.1%) African descent. Mean BMI 26.5 ± 4.8, calf circumference 34.1 ± 4.0. Sarcopenia was found in: 69 (9.8%) [95 CI: 7.8-12.2] with SARC-F; 22 (3.1%) [95% CI: 2.0-4.7] with SARC-F + CC (<31 cm); 31 (4.4%) [95% CI: 3.1-6.2] with SARC-F + CC (<33 cm) and 54 (7.7%) [95% CI: 5.9-9.9] with SARC-F + A + BMI. Gold standard tests such as DXA and other imaging measurements are not available for wide use in communities, especially for economic reasons.

Conclusions
In a group of Colombian women, the presence of sarcopenia was similar, with different versions of the SARC-F. In women in their communities of residence, outside of hospital environments, there were a greater number of women with SARC-F and fewer with SARC-F + CC with a cut-off point of <31, who met screening criteria for sarcopenia.

Poster Session

Topic: 1.1 Regulation of the HPG axis

P001 The effectiveness of different treatments in cycle regulation of women with abnormal uterine bleeding related to ovulatory dysfunction: a single center, retrospective, comparative study in China

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Objective
The aim of the study was to investigate the effectiveness of three different medical treatments in patients with abnormal uterine bleeding related to ovulatory dysfunction (AUB-O).

Methods
In this single center, retrospective study, we analyzed clinical data of 120 patients with AUB-O in our hospital from January 2018 to December 2018. All the eligible patients were divided into three treatment groups according to the different regimens, which was Group A with 3mg Drospirenone/ 20μg Ethinylestradiol Tablets II (DRSP/EE II) treatment for 3 cycles (starting from cycle D1, n=40), Group B with DRSP/EE II treatment for 6 cycles(starting from cycle D1, n=40) and Group C with 10 days of daily dose of 10 mg Dydrogesterone for 3 cycles(starting from cycle D 15, n=40). The effectiveness, adverse reactions and ovulation recovery after stopping treatments were analyzed.

Results
The effectiveness rate of Group A and B were significantly higher than Group C, which was 97.5%, 100% and 62.5% respectively ($p<0.05$). Compared with Group C, the ovulation rate of Group A and B were significantly higher, which was 6.1%, 24.2% and 69.7% respectively ($p<0.05$). During the treatment periods, more patients in Group A (n=31,41.9%)and B (n=40, 54.1%)achieved regular bleeding pattern than patients in Group C(n=3.4.1%), $p<0.05$. The adverse reactions (breast tenderness and dizziness) reports of Group A and B were significantly less than those of Group C, $p<0.05$. In Group A and B, the bleeding duration time and volume were lower than that in Group C, the difference was statistically significant.

Conclusions
DRSP/EE II was more effective than Dydrogesterone in increasing ovulation rate, recovering regular menstrual cycle, decreasing bleeding time and volume in patients with AUB-O. Furthermore, the adverse reactions were lower than Dydrogesterone. DRSP/EE II might be the better choice for the treatment of AUB-O.

Topic: 1.1 Regulation of the HPG axis

P002 Functional test with gonadotropin-releasing hormone analog in the diagnosis of female central hypogonadism

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Context

Central hypogonadism (CH) in female is a syndrome characterized by amenorrhea due to hypoestrogenemia in absence of physiological central (hypothalamo-pituitary) regulation. Diagnosis of this condition is complicated in patient with intact pituitary region and in the excluding of other amenorrhea reasons: there are no reliable diagnostic criteria. In such patients diagnosis is based on measuring of plasma LH and FSH: low concentrations of gonadotropins can be revealed in most of cases. However, LH and FSH within reference ranges do not exclude CH because impairment of impulse secretion can occur despite the normal basal level. A functional diagnostic test will be useful for revealing of impulse secretion insufficiency.

Method

A functional test with a subcutaneous administration of 0.1 mg triptorelin (GnRH analog) was performed. Basal (0 point, before drug administration) and stimulated (1 point, 4 hours after drug administration) levels of plasma LH and FSH were determined. The chemiluminescent immunoassay method was used.

Patients

Female patients with proven CH (n=22, aged 18-37 y.o. Me 22 [21; 29]) and control group – healthy menstruating fertile women (n=10, aged 23-38 y.o. Me 26 [24; 27]).

Main outcome measures

Patients: basal LH 0.1-7.4 ME/l (Me 2.16 [0.93; 3.4]), stimulated LH 0.41-93.3 ME/l (Me 24.4 [9.9; 33.9]); basal FSH 0.19-9.3 ME/l (Me 6.09 [2.9; 6.6]), stimulated 3.2-43.7 ME/l (Me 22.45 [9.1; 27.6]).
Control group: basal LH 1.8-9.66 ME/l (Me 4.94 [3.6; 5.4]), stimulated 24.7-101.9 ME/l (Me 53.05 [38.8; 80.8]); basal FSH 3-11.5 ME/l (Me 7.28 [5.1; 8.1]), stimulated 13.6-48.7 ME/l (Me 22.4 [18.3; 25.7]).

Results

ROC-analysis identified that absolute stimulated LH level ≤35 ME/l pointed to central genesis of hypogonadism with sensitivity 77.3% and specificity 90.0% (AUC ROC curve 0.8364, p=0.0026). Stimulated relative LH has not appropriate reliability. FSH showed low diagnostic value for both absolute and relative stimulated levels (AUC ROC curve<0.6, p>0.1).

Conclusion

A functional test with subcutaneous administration of 0.1 mg triptorelin had a high diagnostic value for the determination of hypothalamo-pituitary genesis of hypogonadism (including cases with “normal” basal gonadotropins’ levels) in female patients with intact pituitary region and in the absence of other amenorrhea reasons. Stimulated LH level ≤35 ME/l can be considered as diagnostic criterion in this situation with sensitivity 77.3% and specificity 90.0%.

Topic: 1.1 Regulation of the HPG axis

P003 Antimüllerian hormone by specific age in a group of Latin American women treated in a fertility center in Mexico

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Context
Antimulllerian hormone has been widely used as an ovarian reserve marker, which helps predict success in reproduction treatments. It is not known if the curves obtained in other countries can be applied to our population

Objective
To determine the values of antimulleriana hormone in a population of women of Mexican origin to graph them according to age groups.

Methodology
Observational, descriptive, retrospective, cross-sectional study

Patients
Angeles Pedregal Hospital´patients from 2008 to 2018, with a report of the antimüllerian hormone level, excluding patients with diseases that alter the level of it, were graphed and analyzed by age group (Final sample: 450 patients).

Intervention
Data collection.

Main outcome measure - Results
The age range was 18 to 48 years, with a mean of 36.93 years and a standard deviation of 5.2. The most frequent reason for consultation was 58.8% primary infertility, with a mean infertility time of 45 months, SD 40 months, with a minimum of 12 months and a maximum of 210 months; As for infertility factors.
The range of the HAM value was from 0.003 ng / ml to 9.4 ng / ml, with a mean of 1.5 ng / ml and a standard deviation of 1.82. Segmentations were carried out by age group, due to the low number of cases under 30 years (that is to say, all cases from 18 to 30 years old were included). Subsequently, antimüllerian values were described for each age. An annual decrease was observed after 40 years, from 0.1 to 0.3 ng / ml. When performing the statistical tests to determine if there was a relationship between age and the HAM level, scatter plots were made to assess the general panorama of the data, finding a wide and not line, so the test was carried out. Kolmogorov-Smirnov finding them with abnormal distribution (p 0.000). In this case, we proceeded to use the Spearman correlation variable for continuous quantitative variables of free distribution, finding a correlation coefficient of -436, with a significance of.000, so it was determined that there was a slight association between age and antimülleriana hormone level as the latter progressed, but if linear (p 0.000).

Conclusions
The determination of the antimulleriana hormone in specific populations is useful and it serves to give personalized recommendations, as well as base of epidemiological studies in favor of an individualized medicine.

Topic: 1.1 Reproductive neuroendocrinology

P004 CA125 level as a predictor for successful implantation in soft stimulation IVF-ICSI cycle: a prospective study

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Purpose

Serum cancer antigen (CA)-125 concentrations has been suggested as a valuable marker for endometrial receptivity and the can predict the likelihood of pregnancy in assisted reproduction. This study aims to determine whether the serum levels of CA-125 in patients undergoing IVF–embryo transfer (ET) promotes favourable outcome in soft stimulation regime.

Methods

Between January 2018 and December 2018, 166 samples of serum CA-125 were obtained on the day of human chorionic gonadotropin (hCG) administration, ovum retrieval (OR), and ET in patients undergoing IVF cycles. Patients were treated with a follicular phase clomiphene citrate and human menopausal gonadotropin.

Results

A total of 149 oocyte retrievals resulted in 143 ETs. Fifty-seven (38.7%) clinical pregnancies (serum bhcg more than 5iu/ml) were recorded. The live-born rate was 26%/OPU and 27.8%/ET. The level of serum CA-125 from the day of hCG until the day of ET did not show any prognostic value to the outcome of IVF.

Conclusions

In IVF-ICSI with soft stimulation regime, there were no significant differences in the level of serum CA-125 concentrations between pregnant and non-pregnant patients and yielded no prognostic value in the likelihood of successful implantation.

Topic: 1.1 Reproductive neuroendocrinology

P005 men in dilemma: a case of persistent müllerian duct syndrome

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A 32-year-old male presented to the accident & emergency with acute onset of right-sided scrotal pain. He had subfertility for four years with no sexual dysfunction and suffered from right scrotal swelling for at least three years with concurrent undescended left testis since birth. The right scrotal swelling measured 8 x 6 cm, which tenders on palpation. The left scrotum was not palpable. A diagnosis of strangulated right inguinal hernia was made, and an emergency right herniotomy was planned. Intra-operatively, an infantile uterus with the elongated cervix, bilateral gonads and fallopian tubes were found to be located deep within the scrotum through the right inguinal canal resulting in a direct hernia. Given complex findings, limited resource and experiences the procedure were abandoned, and he was then referred to our centre where urologist and reproductive endocrinologist was made available to handle this case.

MRI revealed features of right hernia uteri inguinalis, absence of ovaries and vagina with abnormal cystic seminal vesicles. A hormonal profile, biochemical markers and karyotyping revealed all normal result. His semen analysis was not surprisingly showed azoospermia. Subsequently, a combined surgery was proposed for right inguinal repair, hysterectomy and testicular plication. Intraoperatively, an infantile uterus with the elongated cervix, bilateral gonads and fallopian tubes were found within the scrotum through the right inguinal canal. Biopsy of both gonads was done, revealing healthy golden yellow tissue suggestive of testicular tissue. An immediate microscopic examination by the embryologist showed immature spermatozoa and spermatids on the right and the left gonads, respectively. Excision of the uterus, cervix and bilateral fallopian tubes were performed, and the operation was completed with bilateral orchidopexy.

Histopathological examination confirmed the presence of uterus, cervix and fallopian tube. The testicular tissue also confirmed histologically with the presence of spermatogonia with complete spermatocytes arrest equivalent to Johnsen score 3. Based on these findings and confirmed histologically, he was diagnosed as PMDS and counsel for long term management. His emotional was sound, and he was not keen on counsellor assessment. For fertility point couple were offered *in vitro* Fertilization (IVF) with Intra Cytoplasmic Semen Injection (ICSI).

Topic: 1.1 Reproductive neuroendocrinology

P006 Features of gonadotropic and ovarian functions among patients with chronic disorders consciousness

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Context

Chronic disorders of consciousness (DOC) and the possibilities for its correction are an important multidisciplinary problem. As it is known patients with DOC have an amenorrhoea. Restoration of menstrual function is one of the positive prognostic factors, which may correlate with the appearance of consciousness.
Objective is to study gonadotropic and ovarian functions among patients with chronic DOC.

Methods

All patients had an oligomenorrhea or amenorrhea, blood hormone levels are determined once a week three times in a row: FSH, LH, estradiol, progesterone, total testosterone, prolactin. Pelvic and breast ultrasound examinations were performed.

Patients

We examined 9 women with chronic DOC from 20 to 34 years (average age 25.78± 4.94 years). According to the etiology of DOC all women were divided into two groups: patients with hypoxia, 66.7% and non-hypoxic brain damage, 33.3%. The level of consciousness was determined by the Full Outline of UnResponsiveness, FOUR: 44.4% were in a minimally conscious state (MCS) “plus”, 22.2% - MCS “minus”, in an unresponsive wakefulness syndrome - 33.4%. The duration of DOC ranged from 1 to 15 months. 66.7% of patients had normal body weight, but 33.3% of women had an underweight.

Main outcome measure

All patients with chronic DOC were divided on women with hypogonadotropic anovulation - 55.6%, and women with normogonadotropic anovulation - 44.4%.

Results

55.6% of patients with hypogonadotropic anovulation (FSH level <1.5 IU/L), 44.4% - normogonadotropic anovulation. Prolactin levels among 77.8% of patients were within the reference frames, but 22.2% of patients with chronic DOC had hypoprolactinemia. It was noticed that 22.2% of patients had an expressed hypoestrogenemia, when the others had lower limit of normal of estradiol. Endometrial thickness (M-echo) according to pelvic ultrasound examination was from 1 to 3 mm.
Based on statistical analysis, there was not found association between the duration of DOC and the type of ovarian inadequacy (Mann-Whitney test p-value = 0.149). There was no association between the body mass index and the type of ovarian failure, as well as between the cause of chronic DOC and the type of ovarian inadequacy (Fisher’s exact two-way test).

Conclusions

Understanding of hormonal regulation mechanism disruptions in chronic DOC may open prospects for choosing pathogenetically based hormone replacement therapy and improve outcomes in the form of consciousness recovery.

Topic: 1.1 Reproductive neuroendocrinology

P009 From failure of luteal phase to hypothalamic-pituitary-ovarian dysfunction

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Context

In recent years, in women with miscarriage and endocrine infertility, doctors often establish a diagnosis of luteal phase deficiency and therefore do not conduct pathogenetically substantiated therapy.

Objective determine the pattern of endocrine disorders in women with miscarriage and infertility, outline directions in effective therapy.

Methods

The serum levels were determined: FSH, LH, prolactin, androgens, thyroid stimulating hormone, T3, T4, free testosterone, DHEA, luteal progesterone.

Patients

A total of 117 women aged 24-28 years with miscarriage (60) and endocrine infertility (57) were examined.

Intervention Complex treatment for three months was carried out: reduce stress - relaxation techniques in groups of up to 7 people, use herbal medicines - Vitex agnus-castus - 4 mg per day for 3 months; melatonin - 2.5 mg daily for 4 weeks, vitamin B6 - 50 mg per day for 3 months, using acupuncture, stimulation of ovulation- clostilbegit.

Main outcome measures

Pregnancy, delivery.

Results

It was found that the LH / FSH ratio exceeded 2.1 in 47 (78.3%) of 60 women with miscarriage and in 49 (86.0%) of 57 women with infertility. At the time of the examination, women with infertility did not ovulate in 42 cases (73.7%) of 57 and in 12 cases (20.0%) of 60 women with miscarriage. Functional hyperprolactinemia occurred in 38 women (63.3%) with miscarriage and in 29 women (50.9%) with infertility. An increase in testosterone levels was detected in 4 women (6.7%) with miscarriage and in 17 women (29.8%) with infertility. DHEA was elevated in 7 women (11.7%) with miscarriage and in 14 women (24.6%) with infertility. T0he level of thyroid hormones was abnormal in 5 women (8.3%) with miscarriage and in 9 women (15.8%) with infertility. The level of lutein progesterone was within the normal range in all examined with scorching, and in 2 cases (3.5%) in women with infertility. First of all, the data obtained indicate violations in the hypothalamic-pituitary-ovarian axis.

After conducting complex treatment for three months, pregnancy began: in 17 women (29.8%) with infertility, which ended in childbirth in 15 cases (26.3%), in two cases there was a miscarriage; 48 women (80.0%) with miscarriage who ended in childbirth in 45 cases (75.0%), and in three cases there was a spontaneous abortion.

Conclusions

Considering that there are no diagnostic criteria for diagnosing luteal phase insufficiency, and the very concept of luteal phase insufficiency in infertility (miscarriage) does not reflect the essence of pathophysiological changes, since the ovaries do not function in isolation, the concept of luteal phase insufficiency should be abandoned at present.

In infertility (miscarriage), when etiological factors are not clear, but symptoms indicative of endocrine disorders are determined, it is advisable to diagnose hypothalamic-pituitary-ovarian dysfunction.

Topic: 1.2 FSH and LH receptors

P009b Does HP-hMG decrease miscarriage rate vs rFSH in preimplantation genetic testing cycles?

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Context
The role of controlled ovarian stimulation and particularly, the influence of the type of gonadotropin in relation to the proportion of euploid embryos has been little studied

Objective
To evaluate if hCG-driven LH activity of HP-hMG improves clinical outcomes in women of advanced maternal age undergoing a preimplantation genetic testing (PGT-A) treatment
Methods Multicenter retrospective, anonymized cohort analysis performed in 11 Spanish clinics from the IVI group. Patients underwent short GnRH antagonist protocol,0.25 mg daily doses from day 6 of stimulation. On day cycle 2/3, they received daily 150 IU rFSH α/β or HP-hMG with FSH: LH activity ratio 1:1. A single dose of 0.1 mg GnRH agonist was used to trigger final oocyte maturation. Transfer of a euploid embryo was performed in a subsequent cycle. ANOVA and Chi-squared statistical analysis was performed

Patients
Study population included women ≥38 years old undergoing a PGT-A diagnosis cycle with HP-hMG (n=578) or rFSH (n=239).

Interventions
None

Main outcomes measures
Doses of gonadotropin, Number of oocytes, number of metaphases II, usable blastocyst rate per oocyte, metaphase II or fertilized oocyte, percentage of aneuploid embryos, implantation rate, pregnancy rate, miscarriage rate and live birth.

Results
No differences were observed between groups in ovarian stimulation protocol variables, except for significantly lower gonadotropin doses and days of stimulation with HP-hMG vs rFSH: 1794±75 IU vs 2160±25 IU (p<0.001) and 10.5 ± 0.4 days vs 11.5 ± 0.7 days (p=0.040), respectively; rFSH group had a significantly higher number of oocytes (12.3±1.0 vs 10.4±0.6, p=0.001) and MII (10.1±0.8 vs 9.2±0.5, p=0.045) vs HP-hMG group, but in embryo development parameters, results significantly favored HP-hMG (p=0.013) in the usable blastocyst rate per oocyte (35.8%) vs rFSH (31.7%). After the transfer of a single euploid embryo, clinical outcomes were similar for both groups, except for miscarriage rate that was lower (p=0.062) with HP-hMG (7.4%) vs rFSH (11.4%)

Conclusions
Assuming the limitations of a retrospective study design, all things being equal with respect to the transferred embryo since we are always transferring a euploid embryo, these suggest that the administration of HP-hMG in monotherapy improves the results within an advanced maternal age context. Patients using HP-hMG needed fewer days of stimulation, lower doses of gonadotropins and they got a more efficient MII/oocyte ratio with a significantly higher usable blastocyst rate per retrieved oocyte. These results are in line with hCG-driven LH activity, mainly provided by hCG of postmenopausal origin only of this HP-hMG, improving oocyte quality. There is a significant decrease in the miscarriage rate that could be related to a better embryo quality in the case of HP-hMG.

Topic: 1.3 Hyperprolactinemia

P010 When effective medical treatment of a macroprolactinoma fails to correct infertility – a case report of a successful assisted reproduction approach

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Context

Prolactin secreting adenomas (prolactinomas) are common pituitary tumors in women of childbearing age, and usually responsible for anovulation and infertility. Medical treatment with dopamine agonists will very often correct symptoms, reduce tumor size, and allow pregnancy in more than 90% of the cases. Those who remain infertile embodies a unique challenge.

Objective

Report the assisted reproduction treatment approach in a case of a women who persisted infertile despite of a macroprolactinoma's effective medical treatment.

Patient Intervention

A 33 years old women was referred due to primary infertility, with five years of duration. At the age 29 a hyperprolactinemia was found, in the setting of secondary amenorrhea coming from a hypogonadotropic hypogonadism (HH). Cabergolin was started soon after the diagnosis of a macroprolactinoma, with excellent analytical and imagiological response: the prolactin levels became normal within weeks and the tumor became residual in size one year later. However amenorrhea persisted. From the study at admission, to our tertiary center, there was only a slight decreased level of progesterone. Spermogram was normal. An ovulation induction with 112,5 mg/day of Menopur® (LH+FSH) was attempted without success. As the next step, a stimulation with Menopur® 150 mg/day was proposed to perform intrauterine insemination, however it had to be canceled, due to excessive ovarian response. It was then decided to perform *in vitro* fertilization after stimulation with Menopur® beginning at 300 mg/day. One embryo was successfully transferred, resulting in a pregnancy of good evolution.

Conclusions

Given the context of a HH infertility from a prolactinoma, it would be expected that an effective medical treatment would fix the hormonal imbalance, restores menses, and fertility. However despite having normal gonadotropins levels, amenorrhea persisted, with no other obvious etiology. This functional hypothalamic amenorrhea "look alike" imposed a therapeutic challenge. Pregnancy was achieved only after high doses of gonadotropin´s stimulation. This illustrates how difficult is to predict ovarian response, and on the other hand, that women with HH not always require lower doses compared with women who are infertile for other causes. For these reasons early infertility referral to a multidisciplinary team is key for these patients.

Topic: 1.3 Hyperprolactinemia

P011 Kisspeptin level in patients with resistant prolactinomas before and after tamoxifen treatment

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Introduction

Patients with resistant prolactinomas have problems with realization of reproductive function due to chronic anovulation and hypoplasia of an uterus and ovaries. SERM tamoxifen demonstrates a recovery of menstrual function and ovulation and reverses the hypoplasia of the uterus. The mechanism of its action in case of hyperprolactinemia is not clear yet. In study the role of kisspeptin was researched.

Materials and patient

The pilot study included 2 women of reproductive age (30 and 27 years old) with resistant prolactinomas treated by maximal doses of cabergoline 4.5 mg per week. Patients had amenorrea for 6 and 8 months. Tamoxifen was administered in dose 10 mg per day for 3 months. Hormonal and pelvic ultrasonic parameters were evaluated before and after complex treatment.

Result

Before complex treatment, prolactin level was 2658 U/l and 3001 U/l, LH and FSH were normal. At ultrasonography patients presented symptoms of anovulation cycle. There was not any differences between kisspeptin level before and after tamoxifen treatment and its level varied from 0.041 to 0.053 in first patient and from 0.069 to 0.077 in second, p=0.18. Normal menstrual cycle were recovered in 1 month after start of study in both women. Prolactin level decreased without statistical significance. Dynamics of ultrasound picture in 3 months revealed significant melioration of the state of reproductive organs with signs of ovulation like presence of corpus luteum and dominant follicle.

Conclusion

Tamoxifen recovers menstrual function without changes of kisspeptin and prolactin level that may be explained by direct activation of estrogen receptors and positive affects to ovaries and endometrium without recovering of the hypothalamic level regulation.

Topic: 1.4 GnRH analogues and antagonists

P012 Early luteal phase gonadotropin-releasing hormone agonist support before vitrified-thawed embryo transfers during artificial cycles

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Objective

To determine the effect of an additional single dose of gonadotropin-releasing hormone agonist (GnRHa) before embryo transfer on pregnancy outcomes in artificial or non-luteal frozen embryo transfer (FET) cycles.

Study design

A retrospective cross sectional study performed in Medically Assisted Conception (MAC) Unit, Universiti Kebangsaan Malaysia Medical Centre. Women who underwent an artificial FET using standard hormonal replacement therapy (HRT) for endometrial preparation were reviewed from January 2016 to December 2018. Additional of a single dose of 0.2 mg subcutaneous triptorelin was administered 2 days before implantation concurrent with routine progestogen support. Altogether, 202 FET cycles were analyzed after excluding patients with different luteal phase regime, pure or modified natural FET and medical records with missing data. The pregnancy outcome measured includes biochemical pregnancy rates, clinical pregnancy rates, live birth rates, miscarriage rates.

Results

The clinical pregnancy and total live birth rate was lower in the study group (25.8% vs 33.3%, p = 0.282 and 22.7% vs 31.4%, p= 0.206) with higher in total miscarriage rate compared to the control group (7.2% vs 5.7%, p= 0.777), despite not reached statistical significance. The biochemical pregnancy rates were comparable between the groups (42.3% vs 49.5%, p=0.325).

Conclusions

Combination of early luteal phase support with GnRH agonist on the standard progestogen therapy before frozen embryo transfer in artificial cycle is detrimental to total live birth rate with higher in miscarriage rate. A larger randomized controlled studies in the future essential to confirm the result and investigate the specific biologic mechanism.

Keywords: Early luteal phase support, GnRH agonist, live birth rate

Topic: 1.4 GnRH analogues and antagonists

P014 Comparisons of half-does GnRH antagonist versus one-does protocols in IVF accounting for patient type

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Context
GnRH antagonists produce immediate suppression of gonadotrophin secretion. To prevention of premature LH surges in controlled ovarian stimulation for IVF/ICSI, 0.25 mg was used as the minimum daily dose of GnRH antagonist(GnRH-ant).

Objective
To evaluate the effectiveness and safety of half-does GnRH-ant protocol in IVF.

Methods
About 688 consecutive IVF/ICSI fresh cycles were retrospectively analyzed, with 306 in the one-dose GnRH-ant protocol group and 382 in the half-does GnRH-ant protocol group at Creation and Love Women's Hospital from December 2014 to January 2019.

Patient(s)
Separate comparisons were performed for the general IVF population (n=321) and women with poor ovarian response(n=367)

Main outcome measure(s)
The primary outcome was the incidence of premature LH surge, secondary outcomes were the number of retrieved oocytes, the number of viable embryos and the pregnancy outcomes.

Result(s)
In all patient type, the half-does GnRH-ant group showed that the incidence of premature LH surge was not significantly higher than that in one-does GnRH-ant group(2.0 vs. 1.62%, P>0.05). Also, differences were not significant in the number of oocytes retrieved, MII oocyte rate, 2PN embryo rate, viable embryo rate or high-quality embryo rate compared with the one-does GnRH-ant group. In general IVF population, the pregnancy rate was similar between the two groups (53.2 vs. 58.7%, P>0.05). In poor responders, the pregnancy rate showed tend very slightly higher than that in one-does GnRH-ant group(34.2 vs 30.5%, P>0.05) without significant difference.

Conclusions
There is a non significant difference between both protocols regarding prevention of premature LH surge in IVF general population and poor responders. The clinical outcome may be further improved by developing more flexible antagonist regimens taking into account individual patient characteristics.

Keywords: GnRH-antagonist, Half-does, IVF, LH surge, pregnancy rate.

Topic: 1.7 Androgens and hyperandrogenisms

P017 Satisfaction on the use of an oral combined hormonal contraceptive containing 2 mg dienogest/0.030 mg ethinylestradiol (Sibilla®) for the treatment of moderate acne: first results from a Portuguese population.

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Introduction

Acne is the most common chronic skin disease mainly affecting adolescents and young adults. It is a multifactorial disease characterized by androgenic stimulation of sebaceous glands. For this reason, combined oral contraceptives containing anti-androgenic progestogens are suitable candidates for acne treatment.

Objective

This study aimed to evaluate satisfaction and acne severity after 3 and 6 months of use of Sibilla® for the treatment of moderate acne by women in Portugal.

Material and Methods

This was a prospective, multicentric and observational study. The number of acne lesions (either comedones, papules, pustules, or nodules), self-evaluation of acne severity, skin comfort, and satisfaction were assessed after 3 and 6 months. Healthy women between 16 and 45 years of age with mild to moderate facial acne who were going to start Sibilla® as part of their normal acne treatment routine were recruited. Women who were taking contraceptives in the previous 3 months or were medicated with isotretinoin at that time were excluded. Women who were pregnant, with alcohol/ drug addiction, serious illnesses or mental disorder were also excluded. One hundred and three participants were recruited, of which 92 were enrolled in this study. After 6 months, 27 participants were lost to follow-up. For the statistical analysis, repeated measures ANOVA or Friedman's Test were used, with statistical significance set a priori as 0.05. A Bonferroni post-hoc analysis was performed using paired T-test or Wilcoxon test, respectively.

Results

Eighty-four percent of the participants are 16-19 years old, 13% are 20-29 years old, and 3% are over 30 years of age. Sibilla® treatment showed a statically significant reduction in the number of lesions ($p<0.01$) after 3 months. Self-reports on acne severity were reduced, skin oiliness decreased, skin comfort increased, and overall satisfaction with the skin improved after 3 months ($p<0.01$). The aforementioned parameters were all further improved from 3 to 6 months ($p<0.01$), with more than 80% of the participants revealing to be satisfied/ very satisfied with the treatment at these stages.

Conclusions

Outcomes have improved after 3 months of treatment. The results persisted and were even more significant after 6 months, with most women reporting improvements in skin acne lesions and satisfaction with Sibilla®, thus supporting Sibilla® as a valid option for the treatment of acne in women seeking oral contraception.

Topic: 1.7 Androgens and hyperandrogenisms

P018 Fertility and conception in a patient with virilizing adrenocortical carcinoma: a case report

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Context
Adrenocortical carcinoma is a rare virilizing tumor with an estimated incidence of 0.5-0.2 new cases per million annually. Its clinical evolution may include an initial phase of defeminization, followed by masculinization, resulting from increased androgen levels.

Objective
To present a case of virilizing adrenocortical carcinoma culminating to a successful pregnancy, and to present the appropriate diagnostics, management options and issues on future fertility

Method and patients
A case of a virilizing adrenocortical carcinoma is reported in a 33-year-old nulligravid presenting with secondary amenorrhea for 9 months, along with 16-year history of infertility and manifestations of hirsutism and virilization.

Intervention
Dehydroepiandrosterone Sulfate (DHEA-S) and total testosterone were elevated and imaging revealed an adrenal androgen-secreting neoplasm.
Laparoscopic adrenalectomy, right was done.

Outcome
Postoperatively, there was resolution of hirsutism and the virilizing features, menstrual cycles recurred, with decline of serum androgen levels to normal limits. The patient subsequently conceived and delivered to a live term cephalic baby boy via low transverse cesarean section for cephalopelvic disproportion. No fetomaternal complications were noted.

Conclusions
Prognosis is excellent with surgical resection. However, its aggressive behavior and high recurrence rate warrants the need for adjuvant therapy and questions the feasibility of future pregnancy.

Topic: 1.7 Androgens and hyperandrogenisms

P020 The effects of testosterone undecanoate with placebo or dutasteride on muscoloscheletric system and body composition in transmen: a pilot randomized, double-blind placebo-controlled trial

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Context

Gender dysphoria refers to distress caused by a discrepancy between the gender identity and the assigned gender at birth. To align phenotypic characteristics with gender identity features transmen are treated with testosterone (T). The role of T and its metabolite dihydrotestosterone (DHT) on muscoloscheletric system is still largely unknown. In men treated with T and Dutasteride (Du), lean body mass did not change compared to men treated with T and placebo.

Objective

To investigate the effects of T and DHT on body composition, muscle strength and metabolism in transmen.

Patients

12 transmen were included and evaluated at baseline (t0) and at week 54 of T treatment (t1).

Interventions

Twelve ovariectomized transmen received T Undecanoate (TU) 1000 mg i.m. at week 0, 6, 18, 30, 42 with oral placebo (n=6; TU+placebo) or Du 5 mg/day (n=6; TU+Du) in a randomized, double-blind placebo-controlled trial.

Methods

This study was approved by the Medical Ethics Committee of S. Orsola Hospital, Bologna and it was registered on ClinicalTrials.gov. At t0 and t1 the following measurements were performed: isokinetic knee extension and flexion peak torque and handgrip strength; body weight and composition; biochemical, hematological and hormonal parameters. Body composition was measured by dual X-ray absorptiometry.

Results

In the TU+placebo there was a significant increase in the handgrip strength (t0 32.5±4.7 kg;t1 35.0±4.7 kg p= 0.022) but not in the leg strength (t0 52.7±8.9 Nm;t1 57.1±10.3 Nm p= n.s.). In the TU+Du there was a significant increase in leg strength (t0 57.8±6.8 Nm;t1 64.3±7.3 Nm p= 0.047) while handgrip strength did not change (t0 37.5±3.6 kg;t1 37.5±3.0 kg p= n.s.). In comparison with baseline values there was an increase in lean body mass in both groups (t0 43.9±5.5 kg and 46.4±3.4 kg;t1 45.5±4.4 kg p= n.s. and 48.2±3.9 kg p=n.s, respectively TU+placebo and TU+Du). In the TU+placebo there was a decrease in fat mass (t0 17.1±12.6 kg;t1 14.7±12.2 kg p=n.s) instead in the TU+Du fat mass did not change (t0 15.3±7.7 kg;t1 15.7±5.1 kg p= n.s).

There was a significant decline in HDL in both groups (p=0.005 in TU+placebo and p=0.015 in TU+Du) and no significant changes of other lipoproteins.

Conclusions

Our preliminary data suggest that the addition of Du does not significantly change the effects of T on the analyzed end points. Our results suggest that conversion of T to DHT may not be essential for mediating the effects of T on the muscle.

Topic: 1.7 Androgens and hyperandrogenisms

P021 DHEA and sexuality in elderly people

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Gynecology and obstetrics

Astonishing results from a recent German study will be presented at the ISGE2020. Sexual activities, sexual thoughts and intimacy from 60-82 year-olds were compared to younger adults.
The elderly people reported less sexual activity and less intimacy, but not fewer sexual thoughts.
Sexuality is still important for people over 65 years of age.
Dyspareunia is one of the most bothersome symptoms of postmenopausal women with vulval vaginal atrophy (VVA).
VVA causes distress and a decrease in QoL to approximately 50% of postmenopausal women with an increase in pain during sexual activity, a decrease in desire, libido and satisfaction.
VVA diagnosis is made difficult by the low awareness amongst women regarding the pathological manifestations of the postmenopausal period and unwillingness / embarrassment to discuss the symptoms of an intimate character with the expert.
Oral DHEA has been the focus of numerous researchers in anti aging medicine over the years.
The use of a new, locally acting DHEA showed a significant increase in desire, arousal, lubrication, orgasm, satisfaction and improvement in dyspareunia at sexual activity.
Prasterone is the only locally acting DHEA therapy approved as a vaginal pessary for the treatment of VVA in postmenopausal women having moderate to severe symptoms.
Prasterone provides improvements in symptoms from 2 weeks and has demonstrated an improvement in pain symptoms during sexual activity, increase in desire, arousal, sexual satisfaction and orgasm with a manageable safety profile.

Topic: 1.7 Androgens and hyperandrogenisms

P022 The Leydig cell steroid tumor in a postmenopausal woman with clinical and laboratory hyperandrogenism (a case report)

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The incidence of Leydig cell tumors (LCTs) is less than 0.1% of all ovarian tumors. As usual, LCTs are found in postmenopausal women. The diagnosis of LCTs in postmenopausal women is associated with some difficulties and is mainly based on the identification of hyperandrogenemia and clinical signs of virilization, tumor visualization, and morphological confirmation. Benign LCTs require exclusion of other causes of hyperandrogenism, including malignant tumors.

Objectives

The objective is to demonstrate a clinical case of Leydig steroid cell tumor in a postmenopausal woman with late-onset of clinical and laboratory hyperandrogenism.

Methods and results

We present a clinical case of a 55-year-old Caucasian (Russian) postmenopausal patient (age at menopause 47 years) with LCTs of the right ovary, with a moderate increase of total testosterone (7.6 nmol/l) and progressive signs of hirsutism. After clinical examination, lab tests, pelvic ultrasound, and MRI, we performed a laparoscopic bilateral salpingo-ovariectomy. The 1,1 cm in diameter tumor of the right ovary was confirmed as LCT by a morphological investigation, and the Leydig cell hyperplasia was found in the left ovary as well. By the 1st months after surgery, we observed the significant decrease of total testosterone value, reached a normal level by the 3d month of observation.

Conclusions

In the presented case, we observed a benign LCT of right ovary, accompanied with benign hyperplasia of Leydig cells in the contralateral ovary. LCT is a frequent type of such tumors, associated with a good prognosis and normalization of the clinical and laboratory manifestations of hyperandrogenism after surgical treatment, as was shown in our case. It's the issue of importance, that the type of surgery (bilateral salpingo-ovariectomy), performed in our patient, should be recommended (instead of unilateral intervention) as the treatment of choice for postmenopausal patients with LCTs.

Topic: 1.7 Androgens and hyperandrogenisms

P023 Functional hypothalamic amenorrhea: a model to understand the implications of hypoandrogenism in women's sexual function

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Context

The impact of estrogen deficiency on female sexual function is well established, whereas the role of low androgens is less evident due to methodological limits in clinical routine practice.

Objective

To investigate the potential role of androgens in female sexual function we considered women with functional hypothalamic amenorrhea (FHA) with and without underlying polycystic ovary syndrome (PCOS) according to recent guidelines.

Methods

An observational retrospective study was carried out at the Unit of Gynecological Endocrinology, IRCCS Policlinico San Matteo, University of Pavia, over the last five years. Out of 126 women with FHA, we selected those sexually active divided into two phenotypes accordingly to both hormonal and ultrasound pattern: pure FHA (n=36) and FHA-PCOS (n=43). Circulating hormones (FSH, LH, prolactin, TSH, estradiol, androstenedione, total testosterone, DHEAS, cortisol, insulin, free T3) were measured by routine RIA. Self-administered validated questionnaires to investigate sexual function and sexual distress (FSFI and FSDS) were filled in, after giving informed consent. In addition, psychometric measures were used (Body Attitude Test, Bulimia Investigation Test, The State-Trait Anxiety Inventory, The Beck Depression Inventory, Multidimensional Perfectionism Scale).

Main outcome measures

The two FHA phenotypes were superimposable in term of psychometric variables, but pure FHA had lower total FSFI scores (p=.002) and a more frequent diagnosis of sexual dysfunction (FSD, 41.7% vs 11.6%) compared to FHA-PCOS. Pure FHA has significantly lower levels of LH (p<.0001), prolactin (p<.001), estradiol (p<.001), androstenedione (p<.005), DHEAS (p<.002), insulin (p<.001) and FT3 (p<.001). Interestingly, in the overall population of FHA women, LH and androstenedione values were positively correlated with FSFI score (p=.001 and.01 respectively) and were lower in the FSD group (p=0.01 and p=0.02, respectively).

Results

Patients with pure FHA display a high rate of FSD, in spite of similar psychological vulnerability. This data may be explained by a different endocrine milieu in comparison with FHA-PCOS, especially circulating LH and androstenedione levels.

Conclusions

Women's sexual function is multifactorial and psychological dimensions are relevant to a non-organic diagnosis such as FHA. However, the present data point to the possible role of ovarian androgens driven by LH in influencing sexual response, especially in pure FHA.

Topic: 1.8 Primary and secondary amenorrhea

P024 An intricated cause of hypogonadotropic hypogonadism

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A 46 years old patient presenting an hypogonadotropic hypogonadism was referred to the gynaecologic unit for the initiation of an hormonal replacement therapy. A superior temporal quadrantanopia and a left temporal hemianopsia led to the diagnosis of a 20 mm pituitary mass. She was treated by transphenoidal resection for this mass which was found to be a xanthogranuloma. Right after the surgery, she developed a panhypopituitarism with a thyreotropic insufficiency substituted by L-Thyroxine, a corticotropic insufficiency substituted by hydrocortisone, a central diabetes insipidus treated by desmopressine. In her medical history, we notice that the patient has never been pregnant, her menarche was at the age of 14 and she suffered from secondary amenorrhea since then. Her pubertal development and her growth spurt (+14cm, to reach 157cm) were observed at the age of 17, when she quitted her professionnal career in gymnastics after a tibial plateau fracture. Even after the intensive physical practice was stopped, she still presented amenorrhea. She also suffered from pollakiuria since childhood.
Her recent bone mineral densitometry revealed a severe osteoporosis and her spine X-ray multiple vertebral collapses. The endovaginal ultrasound showed an atrophic uterus (22mm long) with an endometrial thickness of 1.4mm and two small ovaries (left 17x8mm, right 18x16mm).
In conclusion, the functional amenorrhea presumably hid the onset of the organic amenorrhea explaining the delay of diagnosis and the severe consequences of the chronic estrogenic deprivation.

Topic: 1.8 Primary and secondary amenorrhea

P025 Combined oral contraceptive as hormone therapy: effect on bone mass of women with premature ovarian insufficiency. Case-control study

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Objective
To evaluate whether combined oral contraceptive (COC) can be used as hormone therapy (HT) to preserve bone mineral density (BMD) in women with premature ovarian insufficiency (POI).

Methods
Study including women with POI using HT [COC group (ethinylestradiol 30mcg associated with levonorgestrel, continuously use), lower dose group (conjugated estrogen (CE) 0.625mg continuous plus medroxyprogesterone OR 17-beta estradiol (E2) 1mg continuous plus norethisterone), higher dose group (CE 1.25mg continuous plus medroxyprogesterone OR E2 2mg continuous plus norethisterone), tibolone 2.5mg group and group without HT], that realized bone densitometry by DXA technique with 2 ±1 year interval. For all of them, the difference between final and initial (delta) BMD values was calculated for lumbar spine (LS), total femur (TF) and femoral neck (FN). For the analysis of the effect of treatments over time, we used Generalized Estimating Equations, with variables without normal distribution transformed into ranks.

Results
A total of 420 densitometries (210 deltas) was analyzed. The women were 30.34 (9.24) years old and the HT was started at 29.67 (9.46) years. The COC group presented improvement in BMD in LS and TF over time, similar to the higher dose group. In LS, there was loss of BMD in the group without HT, lower dose and tibolone group. For FN, BMD reduced in all groups. For TF, there was reduction in the lower dose group.

Conclusions
For the BMD of POI women, continuous administration of COC was superior to the lowest dose HT, similar outcomes to that of higher dose of estrogen.

Topic: 1.8 Primary and secondary amenorrhea

P026 Non-anorectic functional amenorrhea in young women

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Introduction

Functional amenorrhea can appear due to chemical, emotional or physical chronic stress. It is a particular pathology that can lead to complex issues on different aspects of women's health including skeletal system, cardiovascular system and mental disorders.

Objective

To determine the weight increase threshold in order to achieve gonadostat disinhibition during supplemental therapy with analogues of natural estradiol.

The lot is comprised of 78 young women, with ages between 17 and 34, (mean age of 20.65), 56 adolescents (under the age of 21) and 22 adult women of which 6 over the age of 23, with secondary amenorrhea induced by weight loss. They were addressed to our Endocrine Unit, starting January 2012. Inclusion criteria: spontaneous menarche, regular menses prior to the amenorrhea episode, recent history of weight lost, no hormonal preparation used recently. Exclusion criteria: other central or peripheral causes of secondary amenorrhea.

Method

Were performed at first admission, and every 2 months in the following 12 months the following hormonal assessments: FSH, LH, estradiol, progesterone, PRL, TSH, Ft4, anti TPO Ab., serum cortisol, midnight salivary cortisol, creatinine, GFR, TGP, TGO. Intervention: supplemental therapy with analogues of natural estradiol.

Results

The weight loss responsible for secondary amenorrhea was smaller in adolescents than in adult women: 6.8±1.21 kg versus 33.5 ±6.1 kg. The mean BMI was lower in adolescents (20.67±2.18kg/m^{2}sc) than in adult women (24.11±3.9 kg/m^{2}sc). The mean weight loss was 6.5±1.3 kg in adolescents, but 23.4±4.8 kg in adult women. The degree of central suppression was similar: LH 1.15±0.27 mUI/mL, in adolescents, versus 1.28±0.11 mUI/mL, in adult women p=0.67.

Gonadostat disinhibition appeared sooner in weight loos induced amenorrhea (9,5±2.1 months) compared with a mean of 21.2±4.5 months in stress induced amenorrhea. Both in young women and in adolescents, in adult women. Both in adolescents and adult women, the weight increase threshold for gonadostat disinhibition was around 2 kg.

Conclusion

The vulnerability of gonadostat is higher in adolescents, but the recovery of the function apears after a modest weight increase during estrogen supplementation. Stress induced amenorrhea is more resilient to recovery.

Topic: 1.8 Primary and secondary amenorrhea

P028 Sexual Development Disorders (SDD) in patients with primary amenorrhea and/or delayed sexual development

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Context

SDD are rare in common population, but their incidence in selective groups (patients with primary amenorrhea, infertility, etc.) is 10-70 times higher.

Objective

Detection of prevalence and types of SDD in patients with primary amenorrhea and/or delayed sexual development and elaboration of adequate strategy of management for these patients.

Methods and Patient (s)

325 patients with primary amenorrhea and/or delayed sexual development aged 13-35yy. were investigated. In 137 patients (42,2%) SDD was diagnosed. In all patients clinical, genealogical, ultrasound, hormonal, cytogenetic investigations have been conducted. In 48 patients diagnostic laparoscopy, surgical treatment (removal of gonads, creation of neovagina, clitorectomy, correction of urogenital sinus) and hysto-morphological investigation of gonads have been performed.

Result (s)

Most frequent diagnosis in the structure of SDD was gonadal dysgenesis with mosaic kariotype (62,9% in age group 13-19yy and 38,2% in age group >20yy). Complete androgen insensitivity syndrome was observed in 34,5% of adult and 12,2% of adolescent patients. Mullerian agenesis was detected in 13,4% of adult and in 16,4% of adolescent patients. Turner syndrome, mixed gonadal dysgenesis, Swayer syndrome, partial androgen insensitivity syndrome, ovotesticiular disorder were observed rarely.

In 27 patients with 46,XY kariotype and female phenotype gonadectomy was performed and replacement hormonal therapy with female sex hormones prescribed. Pregnancy was achieved by ART in 5 patients with gonadal disgenesis and mosaic kariotype (egg donation) and in 4 patients with Mullerian agenesis (surrogacy). All of them delivered timely healthy babes.

Conclusions

Correct and timely diagnosis of SDD is very important for adequate treatment, prevention of malignisation of intra-abdominal located gonads in patients with 46,XY kariotype, prevention of osteoporosis and cardio-vascular disorders, improvement of quality of life and prevention of psycho-social problems and stigmatization of these patients.

Topic: 1.8 Primary and secondary amenorrhea

P029 Premature ovarian insufficiency and Cushing's disease

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Cushing's disease leads to hypercorticism due to excess ACTH secretion from a pituitary adenoma. The excess cortisol usually inhibits the hypothalamic-pituitary-gonadal axis, leading to hypogonadotropic hypogonadism.

Objective

To present an unusual case of Cushing's disease associated with premature ovarian insufficiency improving after treatment of the pituitary disease.

Patient(s)

The 35-year-old female patient was referred to the endocrinologist for suspicion of Cushing's disease. For the previous 2-3 years, she had experienced weight gain despite a very strict, hypocaloric diet, muscle wasting in spite of regular physical activities, spontaneous fractures and repetitive mycotic infections. She had stopped her contraceptive method 3 months previously, was amenorrheic since and described vasomotor symptoms. Her biology revealed hypergonadotropic hypogonadism and her AMH level was low. Cushing's disease was confirmed and a pituitary microadenoma measuring 4mm was eventually identified.

Intervention(s)

Resection of the pituitary microadenoma was performed transsphenoidally.

Result(s)

After pituitary surgery, the patient developed corticotrope insufficiency as expected, which received adequate substitution. Regular menses were restored and vasomotor symptoms disappeared with biological proof of normalisation of the ovarian function. Several months later, the patient became spontaneously pregnant.

Conclusions

We illustrate an unusual case of Cushing's disease in a young woman with premature ovarian insufficiency that improved once Cushing's disease was cured.

Topic: 1.8 Primary and secondary amenorrhea

P030 Premature ovarian infufficiency and menstrual cycle characteristics

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Context

Premature ovarian insufficiency (POI) is characterized by oligo/amenorrhoea, FSH >25IU/ml, E2 <50pmol/l in women younger than 40. Variable clinical presentation often postpones the diagnosis.

Objective

The aim of our study was to assess menstrual cycles pattern in patients with POI.

Patients

We have evaluated 101 women, age 36.7±5.78 y. FSH=78.81±37.43 IU/L, E2<50pmol/l, with confirmed POI referred to our Clinic between 2014-2018. Menstrual cycles characteristics were defined according to the pattern of cessation: abrupt (amenorrhoea) or gradual. Gradual pattern was defined according to the length as: shortened (<24 days), prolonged (>35 days) or variable (first shortened then prolonged) and according to the quality of menstrual bleeding: normal, scarlet or abundant. Also, we have grouped our patients according to the age: <35 (age 27.9±4.7; FSH= 27.95±4.76 IU/L) and 35-40 (age 37.53±1.90, FSH=37.52±1.89 IU/L) years. Besides aforementioned and the basic anthropometric measurements (height, weight, waist to hip ratio, body mass index (BMI)) we have collected the information about the age of menarche and the age of mother's menopause.

Results

The most frequent pattern of menstrual cessation was gradual ($p<0.001$). However, in the group of patients <35 y. there was substantial number of patients with the abrupt cessation of menstrual cycle. Overall, patients had significantly increased number of prolonged ($p<0.01$) and abundant menstrual cycles ($p<0.01$) compared to other types of menstrual cycle length and quality. When analyzed according to age, there was no significant difference.

According to anthropometric masurements the older group had significantly higher waist ($p=0.025$) and hip circumference ($p=0.030$) and significantly higher BMI (23.29 vs. 20.84kg/m^2). There was no significant difference between the groups according to the age of menarche or age of mother's menopause.

Conclusion

The results of our study show that patients with POI are expected to have gradual onset of menstrual cessation with prolonged menstrual cycles and abundant bleedings. Missed cycle in women <35y. with previously regular menstrual cycles requires endocrine examinations in order to recognize POI on time.

Topic: 1.8 Primary and secondary amenorrhea

P032 The muscle changes of patients with premature ovarian failure in the combined therapy

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Contex
Premature ovarian failure leads to early aging of the organism, age-associated disease may appear at a young age, a decrease of the amount of muscle is a feature of an early aging.

Objective
Studying of dynamic muscle changes of the patients with premature ovarian failure against the backdrop of a combined therapy.

Material
From 2016 to 2018 the muscle dynamics was analyzed by using bioimpedance of body composition by ABC-01 “Medass”. 30 patients aged from 28 to 35 years, with premature ovarian failure on combined therapy, which includes proper nutrition, the physical activity, sex hormone replacement therapy (continuous 17β estradiol 2 mg\dydrogesterone 10 mg.), metformin, cholecalciferoli in therapeutic or prophylactic doses. A control group composed 20 women, from 32 to 35 years, with premature ovarian failure, who are on proper nutrition, the physical activity.

Methods
Bioimpedance analysis of body composition was conducted every 3 months for 24 months.

Results
BMI average of all groups was 26,6 2,3kg\m^2, percentage of muscle was on the lower limit of normal 41,1 0,8%, the proportion of body fat went beyond the norm 38,3 2,8%. The dynamics of patients with combinated therapy being on diet a balanced diet, physical activity, replacement therapy with sex hormone, metformin, cholecalciferoli, there was an increase of the proportion of muscle and it contributed 46,3 1,2% after 24 months, decline of the proportion of fat mass was contributed 31,8 1,3%, BMI 24,9 1,6 kg\m^2. The control group has also evolved a changes, increase in the proportion of muscle contributed 43,3 0

Conclusions
The combinated therapy as balanced diet, physical activity, sex hormone replacement therapy (continuous 17β estradiol 2 mg\ dydrogesterone 10 mg), metformin, cholecalciferoli, leads to significant decrease of patients’ body fat, increase of muscle to the rates in a compare with those who were using physical activity, balanced diet and accordingly, it gives an aesthetic effect, self-confidence, the extension of youth and improve the quality of life.,6%, decline in the proportion of fat mass contributed 35,1 0,7%, BMI contributed 26,1 0,6 kg\m^2.

Topic: 1.8 Primary and secondary amenorrhea

P033 Swyer syndrome: a rare form of genetic-based primary ovarian insufficiency

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Primary ovarian insufficiency (POI) is a condition, which is characterized by amenorrhea, progressive symptoms of estrogen deficiency, and elevated serum gonadotropin levels in cases of young women under 40.
Genetic, autoimmune, metabolic, iatrogenic disorders are the most frequent, identifiable causes of POI. One of the most common chromosomal anomalies associated with POI is Turner syndrome, but other rare genetic-based POI are known as well, like Swyer-syndrome/46,XY complete gonadal dysgenesis.
The aim of the examination was to identify patients with Swyer-syndrome, and to compare them with other patients with 46,XY karyotype. Between January 2005 and December 2019 thirteen patients were registered with 46,XY karyotype at the Department of Obstetrics and Gynaecology, University of Debrecen. During the examination first signs and symptoms; blood test results, especially LH, FSH, E2, T levels; ultrasound examination results; surgical interventions; and therapy methods were collected.
We registered eight patients diagnosed with Swyer-syndrome, and five patients diagnosed with complete type of AIS (C-AIS), which is also called as Morris-syndrome in the scientific literature. First signs were delayed puberty and primary amenorrhea in both groups, but in the group of Swyer-syndrome withdrawal bleeding could be induced by using medical treatment. During the speculum examination vagina and cervix were visible in this group, and in contrast with patients with C-AIS uterus and vagina were verified with ultrasound. According to the laparoscopic operation streak gonads were found in the pelvic cavity. In the group of C-AIS patients we registered inguinal or abdominal testes and the absence of uterus with ultrasound, which was confirmed with gonad biopsy. Besides these signs clitoromegaly and/or short blind-ending vagina was visible during the gynaecological examination.
The clinical management of patients with 46, XY karyotype includes hormone-replacement therapy and surgical intervention mainly because of the gonad biopsy considering the possible gonadectomy. In addition to these, other treatment methods can be applied in the therapy of either Swyer syndrome or C-AIS.
It is important to separate these disorders because of the exact diagnosis and targeted therapy. The most important differences between the above mentioned conditions will be presented with some clinical cases.

Topic: 1.9 Polycystic ovary syndrome

P034 *In vitro* Fertilization (IVF) pregnancy outcome from two cohorts women: Polycystic Ovarian Syndrome (PCOS) women and unexplained infertility

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Study Objective
To compare the IVF pregnancy outcomes between PCOS women and those who were unexplained subfertility including clinical pregnancy, miscarriage rate, multiple pregnancy rates, and neonatal outcomes

Materials and Methods
A retrospective case-control study involving one hundred eighty-two women was conducted. Ninety-three women with PCOS (study group) and eighty-nine women with unexplained subfertility (control group) who underwent IVF in MAC Unit, UKM Medical Centre from January 2012 until December 2016 were included. Pregnancy outcomes such as preterm delivery, gestational hypertension, gestational diabetes mellitus, instrumental delivery, caesarean section, macrosomic baby, neonatal intensive care unit admission, APGAR score, neonatal hypoglycaemia and neonatal jaundice were analysed.

Results
The study group had significantly more take-home babies as compared to the control group (17.2% vs 10.1%, p=.047). The incidence of gestational hypertension (p=.472), rates of preterm delivery (p=.657), gestational age at delivery (p=.493), and mode of delivery (p=.441) were similar in both groups. There was a significant difference in the incidence of gestational diabetes mellitus (GDM) between the study and control groups (p=.023). There was no statistically significant difference in birth weight, Apgar score at 5 minutes, cord pH, neonatal intensive care unit admission rates, neonatal hypoglycaemia, and neonatal jaundice (p>0.005) between the two groups.

Conclusion
Despite a higher incidence of GDM during pregnancy, there was still higher rates of take-home baby among PCOS women.

Keywords: Polycystic ovarian syndrome, obstetric outcomes, in vitro fertilization (IVF).

Topic: 1.9 Polycystic ovary syndrome

P035 Low antimüllerian hormone (AMH) among polycystic ovary syndrome (PCOS) women: is that possible?

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Introduction

AMH level is known to be higher among the Polycystic Ovarian Syndrome (PCOS) women, who diagnosed based on Rotterdam criteria. However, by using these criteria, emerging evidence revealed an overdiagnosis as PCOS among women with primary ovarian failure (POF). These findings can be distinguished by evaluating the AMH level, however, due to cost, it is not widely recommended by the international board. Therefore we added AMH evaluation among women who underwent fertility treatment and failed to respond appropriately following a standard ovarian cycle stimulation to identified potential over-diagnosed PCOS. Our aim is to identify the incidence of women who label as PCOS following these criteria with low AMH level.

Materials and methods

This is a retrospective study conducted in our centre starting from May 2015 until May 2017. All files of women with PCOS were trace during the study period. The cohort patients who revealed low follicular count following standard ovarian stimulation had their AMH level reviewed and the result was analysed using SPSS version 21.

Results

A total of 376 PCOS women case files was reviewed with the mean age of 33.37, and most of them were obese with a mean BMI of 28.01 kg/m^2. From this 376 patients, a total of 71 women found to have low follicular count despite standard dosage of Controlled Ovarian Hyperstimulation (COH) thus supplemented with AMH level. At least 54 patients were found to have a low AMH level with the lowest was 5.5 pmol/l. Further analysis of fertility outcome showed no significant associated with the level of AMH; (biochemical pregnancy; $p>0.05$, clinical pregnancy; $p>0.05$, numbers of miscarriage $p>0.05$)

Conclusion

The level of AMH should be evaluated among women who diagnosed with PCOS with poor ovarian respond during ovarian cycle stimulation. This allows us to differentiate the possible hidden diagnosis of premature ovarian failure instead of PCOS following the Rotterdam criteria. This also acts as a guide for a clinician in planning fertility treatment.

Keywords: Infertility, primary ovarian insufficiency, women

Topic: 1.9 Polycystic ovary syndrome

P037 Association of hirsutism and hiperandrogenism in patients with polycystic ovary syndrome at the ginecological endocrinology clinic in the Hospital Juárez de México

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Introduction

Hyperandrogenism affects 5% to 10% of women of reproductive age in different regions of the world. Hirsutism is considered the main clinical indicator of androgen excess and occurs in up to 45% to 85% in patients with Polycystic Ovary Syndrome (PCOS). Within the hair follicle, testosterone, under the influence of the enzyme 5α-reductase, becomes in dihydrotestosterone (DHT), which converts hair into terminal hair. There are several studies that have reported a correlation between hirsutism and elevated levels of different androgens, however the findings presented are inconsistent.

Objective

To determine the association between hirsutism and elevated levels of the different androgens in blood (delta 4 androstenedione (A4), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S) and total testosterone (TT) in patients with PCOS.

Study design

A prospective and cross-sectional study of cases and controls was conducted in which 136 patients with hirsutism and diagnosis of PCOS were studied and 68 patients with PCOS without hirsutism. Each group was studied its association with serum androgen levels. The association of the different variables was established through the Odds Ratio (OR).

Results

204 patients were recruited. The results of high androgen levels in the group with PCOS and hirsutism, 73% (n = 99) had elevated delta A4, 5.1% (n = 7) had elevated DHEA, 25.2% (n = 34) High DHEA-S and 13.2% (n = 18) high TT. In the control group, an elevation of delta A4 was reported in 27.9% (n = 19), and only 5.8% (n = 4) of the patients presented elevation of DHEA, DHEA-S and TT. An OR of 6.9 (7.1 – 6.6) was obtained for the association of hirsutism and delta A4, an OR of 0.8 (1.33 – 0.27) for the association of hirsutism and DHEA, an OR 5.3 (60.6- 0.5) for the association of hirsutism and DHEA-S and an OR 2.4 (2.48 -2.36) for the association of hirsutism and total testosterone.

Conclusion

In the Mexican population, women with PCOS with hirsutism have a higher risk of presenting elevated levels of delta 4 androstenedione than women with PCOS without hirsutism, which differs from other populations studied.

Topic: 1.9 Polycystic ovary syndrome

P038 Metabolic changes and first sexual intercourse in adolescents with PCOS in a greater Buenos Aires population

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Objectives

To determine the number of adolescents (12-17 years) between 1/2/17 to 12/31/18 in two medical centers, and the percentage of PCOS' patients.

To establish the percentage of adolescents with PCOS and and the relation with their lipid profile, HOMA, and First Sexual Intercourse (FSI)

Compare the results with the group of adolescents without PCOS.

Material and Methods

Population: Consecutive review of 590 medical records of adolescents between 1/2/17 and 31/12/ 18.

Design: Retrospective, Comparative, Case- control model

Exclusion criteria: Patients that had not completed the requested laboratory

Samples:

Consecutive review of 590 records. 527 records were selected.

Variables: Age, Menarche, FSI, Cholesterol >200mg, Triglycerides>140mg, HOMA>3,5, Hypertension and BMI> 25.

Statistics: Percentage, Media, Range, 2.

Alfa error: 0,05 Beta error: 0,10

Results

N:526 Adolescents. Groups: Group A (GA): Adolescents with PCOS: 46 (8,7%); Group B (GB): Adolescents without PCOS: 480 (91,3%).

FSI:GA:10 (21,7%); GB: 276 (57,5%); 2.: 20,2; p: 0,0001; OR: 0,2; IC: 0,1-0,42

Cholesterol: GA: 12 (26,8%); GB: 52 (10,8%); 2.: 7,7; p:0,01; OR: 2,9; IC: 1,42- 5,9

Triglycerides: GA: 18 (39,1%); GB: 68 (14,1%); 2.: 17,3; p<0,0001; OR: 3,9; IC: 2,08- 7,43

HOMA: GA:24 (52,1%); GB: 68 (14,1%); 2.: 42,01; p<0,0001; OR: 6,6; IC: 3,51- 7,43

BMI: GA: 34 (74%); GB: 162 (33,7%); 2.: 14,92; p: 0,00001; OR: 3,81; IC: 1,92- 7,5

Hypertension: GA: 2 (4,3%); GB:4 (0,084%); 2: 2,18; p: 0,13; OR: 5,68; IC: 1,01-31,12

Conclusions

Adolescents with PCOS represented 8,7% of our study population. We found a statistically significant association betweeen dyslipidemia and obesity in adolescents with PCOS, as well as a high percentage of adolescents with PCO that do not report FSI in this study population.

Topic: 1.9 Polycystic ovary syndrome

P039 PCOS susceptibility loci in Russian population

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Federal State Budget Institution "National Medical Research Center for Obstetrics, Gynecology, and Perinatology named after academician V.I.Kulakov" of the Ministry of Healthcare of Russian Federation

Context

PCOS is a complex reproductive disorder with genetic predisposition. Up to 70% of PCOS pathogenesis could be explained by genetic influences. It is supposed that genetic approach could be useful for diagnostics in adolescents and in case of incomplete phenotypes.

Objective

To evaluate molecular genetic markers of PCOS and its different phenotypes.

Methods

Transvaginal sonography, androgen profile assessment, oral glucose tolerance test (GTT). SNPs were identified by PCR or NGS for 46 loci, associated with IR, impaired folliculogenesis and androgen biosynthesis. Statistic analysis was carried out with IBM SPSS Statistics 21.

Patients

163 women (mean age – 25.2±4.6 years, mean BMI – 23.9±5.3 kg/m^2) with PCOS (Rotterdam criteria, 2003) and 160 healthy controls (mean age – 49.8±7.9 years, mean BMI – 27.4±5.8 kg/m^2) without history of PCOS or endocrine infertility were enrolled. Patients were divided into 2 subgroups: the 1st – with androgen phenotypes (73%), the 2nd – with nonandrogenic phenotype (27%), comparable by age and BMI.

Intervention: blood sampling and genotyping.

Main outcome and measure: allele and genotype frequencies.

Results

PCOS was associated with polymorphism of 6 loci. C/C genotype of SLCO1B1 (rs4149056) and C allele of Rub5B/SUOX (rs705702) were associated with 4-5-fold increase risk of PCOS ($p<0.05$), C/C genotype of THADA (rs12468394), G/G and A/G genotypes of YAP1 (rs1894116), A/A genotype of OCT1 (rs6282031), A/A and A/G genotypes of DENND1A (rs10818854) – with 2-3-fold increase risk of PCOS ($p<0.05$).

A/A and A/G genotypes of IRS1 (rs1801278) and C/T genotype of LHCGR (rs12470652), C allele of FSHR (rs2349415) were associated with increased risk of androgenic phenotype ($p<0.05$).

C-carriers of Rub5B/SUOX (rs705702) had higher fasting glucose and cholesterol level in PCOS patients ($p<0.05$). Patients with G/G genotype of YAP1 (rs1894116) was associated with higher total testosterone level and FAI ($p<0.05$), G-carriers had higher gynoid fat and fasting insulin level ($p<0.05$). A/A genotype of OCT1 (rs6282031) was associated with higher glucose and insulin levels in 1 hour after GTT starts ($p<0.05$).

Conclusion

6 genetic variants were observed as PCOS risk factors in Russian population. 2 loci were associated with androgenic phenotype. These PCOS susceptibility loci are likely to play an important role in etiology of the syndrome.

Topic: 1.9 Polycystic ovary syndrome

P040 Successful conception of a PCOS patient induced by pulsatile GnRH after failed ovulatory induction using letrozole: a case report

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Objectives

To induce ovulation in patients with polycystic ovary syndrome (PCOS) now more and more is recommended to use letrozole. Indeed, we often have good success in our department, treating every day about 200 patients with PCOS who want fertility. However, sometimes this treatment is not successful.

The pulsatile gonadotropin releasing hormone (GnRH) is a therapeutic approach for induction of follicle growth according to the physiological regulation mechanism of hypothalamus-pituitary-ovary (HPO) axis. At present, the technology has been applied in the treatment of idiopathic hypogonadotropic hypogonadism (IHH), central secondary amenorrhea. Until now this technique, however, is rarely used in PCOS. We applied pulsatile GnRH to treat a special obese patient with PCOS and infertility for whom we failed to achieve ovulation using letrozol. Aim is to report about this case.

Methods

A 31-year-old female has a history of natural pregnancy and childbirth, no other diseases. BMI 29.9 kg/m^2. Because she wanted a second pregnancy, she was treated during six cycles with letrozole, 5 mg per day for 5 days, from day 3 to day 7. Within the first three cycles ovuluation was achieved, but not within the next three cycles. Thereafter pulsatile GnRH was given by subcutaneous pulse injection of gonadorelin analogue (pulse every 90 minutes, 6 μg subcutaneous infusion each time). Follicular growth was monitored regularly by B-ultrasound, and the dose of pulsatile GnRH was adjusted gradually. It ended up at 22 μg / 90 min.

Results

After only one pulsatile GnRH given at day 36 of cycle, the dominant follicle on the left grew to 2.17 × 1.91 cm. We used Human Chorionic Gonadotropin (HCG 5000 IU) to induce ovulation, and the woman got within two months naturally pregnant. All the treatments were performed without any relevant side effects.

Conclusion

Since this patient became naturally pregnant, we suggest that pulsatile GnRH therapy can be used during ovulation induction treatment followed by spontaneous pregnancy in letrozole-refractory PCOS patients, providing an ovulation induction program for PCOS patients.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals' Ascent Plan, code: DFL20181401

Topic: 1.9 Polycystic ovary syndrome

P041 The influence of insulin resistance and body mass on lipid profile and liver enzyme in hyperandrogenic women with polycystic ovary syndrome

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Context

Polycystic ovary syndrome (PCOS) is associated with both reproductive and metabolic abnormalities. Abnormal lipid profile as well as increased prevalence of non-alcoholic fatty liver disease (NAFLD) are common in women with PCOS. Obesity and insulin resistance are considered as the main factors related to NAFLD in PCOS. Moreover, existing data suggests that androgen excess, which is the main feature of PCOS and is interrelated to insulin resistance, may be an additional contributing factor to the development of NAFLD and increased cardiovascular risk in PCOS.

Objectives

The aim of our study was to investigate relationship among BMI, insulin resistance, lipid profile and liver enzymes in hyperandrogenic women with PCOS.

Patients and methods

This observational cross-sectional study examined insulin resistance (HOMA IR), lipid profile and liver enzymes in 104 hyperandrogenic women with PCOS (BMI 19-45 kg/m^2, age18-42yrs).

Results

Significant positive correlations were seen between BMI and triglycerides ($r=0.456$, $P \leq 0.001$), BMI and ALT ($r= 0.441$, $p = 0.002$), BMI and gamma GT ($r= 0.410$, $P=0.004$), BMI and FAI ($r=0.548$, $p <0.001$) and BMI and HOMA IR ($r=0.561$, $p<0.001$). Significant negative correlations were obtained between BMI and SHBG ($r=-0.555$, $p<0.001$). HOMA IR showed significant positive correlations with triglycerides ($r=0.511$, $p<0.001$), with ALT ($r=0.386$, $p=0.007$), with gamma GT ($r=0.351$, $p=0.017$), with FAI ($r=0.382$, $p<0.001$). Significant negative correlations were obtained between HOMA IR and HDL cholesterol ($r=-0.378$, $p=0.002$). There was no correlation between androgens (testosterone, androstedione and DHEAS) with lipid parameters or liver enzyme but there was significant positive correlation between SHBG and HDL cholesterol ($r=0.464$, $p <0.001$) and significant negative correlation between SHBG and triglycerides (-0.385, $r=0.001$), SHBG and ALT ($r=-0.354$, $p=0.014$), SHBG and gamma GT ($r=-0.426$, $p=0.003$). Also, significant positive correlation exists between SHBG and HOMA IR ($r=-0.347$, $p<0.001$).

Conclusion

This study confirmed that BMI and insulin resistance could be the most important factors correlated to dyslipidemia and risk for NAFLD in hyperandrogenic women with PCOS.

Key words: polycystic ovary syndrome; insulin resistance; obesity; lipid profile, liver enzyme, NAFLD

Topic: 1.9 Polycystic ovary syndrome

P042 Role of polycystic ovary syndrome and obesity in morbidity pattern among women with endometrial cancer applied for assisted reproductive technologies

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There is no generalized information about morbidity pattern of PCOS and obesity among women suffering from both infertility and endometrial cancer grade I or atypical endometrial hyperplasia in available literature.

Objective

Presentation frequency of occurrence of PCOS and obesity among patients with endometrial cancer grade I or atypical endometrial hyperplasia directed for fertility preservation treatment.

Matherial and methods

97 patients undergoing fertility sparring treatment of atypical endometrial hyperplasia (I group) and endometrial cancer grade I (II group) in reproductive age. Average age of this patients was 36,9 years. All of them suffered from infertility and were directed to reproductologist to be consulted about fertility preservation or pregnancy achievement. 45% of women with endometrial cancer grade I had PCOS, and 48% - visceral type of obesity. In the group of women with atypical hyperplasia the percentage of both PCOS and obesity amounted to 48%. Among 31 women, performed IVF programs, 8 underwent ovulation stimulation, collection and cryopreservation of oocytes / embryos for the delayed reproductive function, after which the treatment of the underlying disease was started or continued. 21 patients underwent an IVF program with embryo transfer in the "fresh cycle" after completing the treatment of cancer and achieving stable remission. 42 patients were excluded from the study due to different medical issues.

Results of the study

PCOS with severe endocrine-metabolic is diagnosed in 46,3% of cases, which makes it necessary to develop programs aimed at preserving reproductive material and treatment methods that reduce the risk of cancer recurrence. High percentage of recurrence (14,2% in women of I group and 30,5% in II group) may be connected with the presence of PCOS and high BMI, because among women, obesity is more strongly associated with the development of endometrial cancer than any other cancer type. This association has been well established and follows a dose-response relationship, with the incidence of endometrial cancer increasing as body mass index (BMI) increases. During fertility preservation program, oocytes or embryos were obtained and cryopreserved in all patients. However, the high risk of cancer recurrence makes it necessary to develop treatment methods aimed to prevent recurrence in this group of patients.

Topic: 1.9 Polycystic ovary syndrome

P042b. Polycystic Ovary Syndrome (PCOS) is more than a fertility issue - Can lifestyle change and reducing weight solve the infertility problem?

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Context

Obesity, irregular menstruation, fertility issues, and hair/skin problems as main-factors for PCOS don't reflect every symptom of PCOS. Insulin resistance, hypercholesterolemia and reduced metabolism lead to far-reaching implications. Throughout a woman's life, PCOS is present, actual without curing. Is normal weight important to conceive? Do endurance excercise play a major role in combination with optimal supply?

Objective

Effectiveness of weight reduction and lifestyle change on fertility.

Method

Pilot-Case Study, DEBEC-Systematic (Diagnostics-Eating-Balance-Exercise-Coaching) steering physical activity, dietary change, holistic coaching. Period: 24 months, Endpoint: 15 kg weight-reduction and lifestyle-adaption. Measuring: weight (kg) and girth of waist (cm), hip (cm), neck (cm), BMI, body fat (in %), waist-hip ratio (WHR). Blood test: hormonal status, cholesterol, triglyceride, fasten glucose. Review after 36, 48, 60, 72 months to emblaze sustainability of DEBEC-Method.

Patient

Case Study, diagnosed with PCOS, age 20, student, overweight 20 kg, high-level androgen and lipid profile, anovulation, acne, hirsutism, no insulin resistance, lifestyle deficits. Fewer sports, fast food user, fatigue and psychological issues e.g. less self-confidence

Intervention

N.A.

Main Outcome

After 24 month's therapies: weight reduction 17.1 kg (11 kg within 12 months). Blood test: normal hormonal status (under birth control pill), normal blood sugar level but cholesterol and triglyceride are out of specification (OOS). Contraceptive: Try and Error with Birth Control pill related to side effects. Personal: motivated, full of energy, success within her studies. Psychological: learned accepting PCOS. Review after 36, 48, 72 months cholesterol was still OOS and weight was 61±2 kg (BMI 22.8±1.5).
Review after 48 month showed a cycle from 21 to 44 days with ovulation signs as mucus in the middle of the cycle. With weight stability and BMI 23, she spontaneous conceived in review period 72.

Conclusion

Normal weight (BMI <25) and lifestyle change with standardized conditions increase requirements to ovulate and conceive.
DEBEC-Methode® shows how an individual based therapy with defined modules and can be successful related to health risk reduction suitable for daily use. This Pilot Study also showed the importance of Coaching. Broader evidence based long-term studies necessary to fulfill individual requirements of PCOS-Patients with the DEBEC-Method.

Topic: 1.9 Polycystic ovary syndrome

P044 Effect of vitamin D deficiency on estrogen, insulin and acetylcholine induced vasodilatation and receptor expression of large vessels in rat model of polycystic ovary syndrome

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Objective

Polycystic ovary syndrome (PCOS) is a common hyperandrogenic condition in women of reproductive age and often associated with vitamin D deficiency and increased cardiovascular risk. In this study the effect of hyperandrogen status and vitamin D deficiency were investigated on the relaxation capacity of large vessels in an animal model.

Methods

Female Wistar rats were treated as follows: 1. (control) group: vitamin D supplemented (3000 IU/kg/week; D+T-); 2. group: vitamin D deficient (<5 IU/kg/week; D-T-); 3. group: vitamin D supplemented with 8 weeks of transdermal testosterone application (D+T+) and 4. group: vitamin D deficient with transdermal testosterone (D-T+) (n=12-12). Aorta rings were measured with wire myograph: estrogen, insulin and acetylcholine induced vasodilatation. Receptor densities (estrogen, vitamin D, insulin, eNOS) of the aorta rings were measured by immunhistochemistry from methanol-fixed sections.

Results

Estrogen, insulin and acetylcholine-induced vasodilatation of the aorta rings were significantly decreased in both vitamin deficient groups compared to the vitamin supplemented groups. Aorta estrogen receptor density was significantly lower in the two vitamin D deficient groups compared to the other two groups. Aorta endothelial IR expression was significantly higher in the vitamin D deficient group, meanwhile in the testosterone treated groups (D+T+; D-T+) the expression was significantly lower. Vitamin D receptor density was significantly higher in the vitamin D deficient groups in comparison to the supplemented groups.

Conclusion

Hyperandrogenic state could occur endothel dysfunction – double noxa might be additive however, adequate vitamin D blood serum level could be a defender factor.

Topic: 1.9 Polycystic ovary syndrome

P045 Tolerability of Ethinyl Estradiol/Cyproterone Acetate (EE/CPA) in the management of PCOS patients

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Objective

Ethinyl Estradiol/Cyproterone acetate (EE/CPA) is widely used in polycystic ovary syndrome (PCOS) patients, but data are rare regarding its effect on blood pressure, carbohydrate and lipid metabolism, liver and kidney function.

Methods

59 patients with PCOS; EE/CPA for 3 cycles. Besides anthropometric indicators and sex hormones, before and after treatment blood pressure and parameters of carbohydrate and lipid metabolism, liver and kidney function were evaluated.

Results

Weight, body mass index (BMI), waist circumference (WC), hip circumference (HC) were significantly lower compared to before pretreatment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed no statistical differences. Carbohydrate and lipid metabolism: No significant difference in total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), insulin (FINS) and homeostasis model insulin resistance index (HOMA-IR), fat distribution and percentage of fat compared to before pretreatment. Serum luteinizing hormone (LH), free androgen index (FAI) decreased significantly. Sex-hormone-binding-globulin (SHBG) increased significantly. Total testosterone (TT), dehydroepiandrosterone sulfate (DHEA-S), androstenedione (AND), free testosterone (FT), serum follicle stimulating hormone (FSH) levels were not significantly different. Liver and kidney function: Blood urea nitrogen (BUN) was decreased, but no significant difference in serum creatinine (CRE), alanine aminotransferase (ALT), AST (glutamic oxalate aminotransferase), glutamyl transpeptidase (GGT).

Conclusion

EE/CPA reduces LH, i.e. is acting like a contraceptive pill (which is not in the labelling!), can decrease hyperandrogenemia and increase SHBG, with the consequence that free testosterone is decreased, both very positive in the management of PCOS. In addition, weight can be decreased. EE/CPA in PCOS elicits no significant negative impact on carbohydrate and lipid metabolism, blood pressure, liver and kidney function. Thus pretreatment with EE/CPA in PCOS patients wanting fertility is a good option in the management for PCOS and has been included in the routine practice of our department.

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Supported by the National Natural Science Foundation of China (grant number 81671411)

Topic: 1.9 Polycystic ovary syndrome

P046 Three ovarian torsions in a prepubertal girl with precocious polycystic ovarian appearance

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Context
Polycystic Ovary Syndrome (PCOS) usually starts in the adolescence and frequently coexists with Metabolic Syndrome. However there is little knowledge about prepubertal PCOS.

Objetive
To report a case of precocious polycystic ovarian appearance and tree ovarian torsion in a same prepubertal girl.

Methods
A case report

Patient
A 10-year-old prepubertal girl had three episodes of right ovarian torsion in a 24 months period (between 10 and 12 years old).

Intervention
All these three acute pain episodes were treated via laparoscopy. In the first episode bilateral polycystic ovarian appearance were identified and they were larger for a prepubertal girl. The right ovary was twisted without necrosis. The treatment at that time was a laparoscopic detorsion only. At the second time, in addition to detorsion, she was submitted to a right ovarian fixation. Unfortunately after two months the right ovary twisted again and a new detorsion and ovarian fixation were necessary.

Results
At that moment the girl had not yet undergone puberty (M1P1). She was 153 cm, 57 kg, BMI 24.35 kg/m^2 (Percentil 97), abdominal obesity, blood pressure 148 x 86 mmHg. No acne neither hirsutism was observed.
The laboratory exams in that moment where: FSH=0.8 mUI/ml; LH=<0.1mUI/ml, E2=5 pg/mL, TSH=3.4 mUI/L, Total Testosterone=9 ng/dL, Insulin=25 mUI/mL, Total Colesterol=245 mg/dL, HDL=39 mg/dL, Triglycerides=154 mg/dL, Glucose= 82 mg/dL, 2h fast glucose test= 101 mg/dL.
The Pelvic ultrasound identified: uterus=3.3x1.9x1.6 (5.0 ml), right ovary 6.5 ml and the left one 9.6 ml with polycystic appearance. Now she is 16 years old and has maintained the polycystic ovarian appearance. The pelvic ultrasound identified right ovary= 17.8ml, left ovary=19.4 ml and the uterus= 24ml. The menarche was at 13 years old and until now the menstrual cycles are oligomenorrheic.

Conclusion
In this case probably the cause of the polycystic ovarian appearance even in a prepubertal girl was the Metabolic Syndrome with Hyperinsulinism and these larger ovaries could favored the torsion.

Topic: 1.9 Polycystic ovary syndrome

P048 The effect of vitamin D replacement therapy on insulin resistance and hyperandrogenism in adolescents with polycystic ovary syndrome

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Context
Several studies have shown an association between low 25(OH)D levels and insulin resistance in obese and type 2 diabetic patients.

Objective
The aim of this study was to investigate chages in insulin resistance markers and hormone alterations in adolescents with PCOS after VIT D treatment.

Methods
We measured body mass index, body fat percentage, serum 25(OH)D, leptin/adiponectin ratio, HOMA index, HDL, triglycerides FSH, LH and free testosteron levels, before and after vit D tretment.

Patients
We analized 51 patient with PCOS, age 16,8±1,1, at the admission and 3 months later.

Interventions
We treated them with 4000IU VIT D daily, for 3 months, as an only medication.

Main outcome measures
Vit D therapy improves insulin sensitivity, there is a significant association between insulin resistance markers and 25(OH)D levels.

Results
3 months after terapy 25(OH)D levels increased from 17.3±6,3 to 39,1±9,2ng/ml (p=0,029), HOMA index decreased from 4,98±0,42 to 3,35±0,45, leptin/adiponectin ratio decreased from 7,39±0,003 to 5,98±0,003 and triglycerides from 2,32±0,32 to 1,68±0,027mmol/l. There were no significant changes in BMI, BF%, FSH, LH and free testosterone levels.

Conclusions
Correcting 25(OH)vit D levels improves insulin sensitivity but does not improve hyperandrogenism in patients with PCOS.

Topic: 1.9 Polycystic ovary syndrome

P049 Diverse spectrum of presentation of infertile women with Polycystic Ovary Syndrome (PCOS) attending Gynae Outpatient Department (OPD) of a tertiary care hospital, Dhaka

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Context
The Polycystic Ovary Syndrome (PCOS) first reported in the classic paper of Stein and Leventhal in 1935 is a heterogenous collection of signs and symptoms that gathered together form a spectrum of disorder from mild to severe.

Objective
The study is aimed to evaluate the different spectrum of presentations in infertile PCOS women attending Gynae OPD at BSMMU.

Materials and Methods
This cross sectional observational study was done from the period of July 2012 to December 2012 among all the infertile women with PCOS attending Gynae OPD at BSMMU. Patients: Due to financial and time constraints only 55 infertile women with PCOS were selected during study period who attended gynae OPD at BSMMU.

Interventions
No interventions were taken as it was an observational study.

Outcomes
The characteristics of women recruited, showed that 50.91% of them were between 21 to 25 years, 54.54% were obese, 67.27% PCOS women were suffering from primary subferility, the commonest second complaint was hirsuitsm (89.09%). Oligomenorrhoea was present in 80% cases, amenorrhoea in 12.73% and only 7.27% had regular menstrual cycle. Hypothyroidism was detected in 16.36% and DM was in 10.9% participants. 5.45% were found hypertensive. 69.09% women demonstrate frank elevation in circulating free testosterone. Serum LH was elevated (> 11.6 ul U/ml) in 56.36% cases and serum prolactin was elevated (< 25 ng/ml) in 16.36%. Only in 3.64% cases serum FSH level was found low (< 2.8 ml U/ml). TVS appearance of polyscystic varies was reported in 76.36% of the patients.

Conclusion
From the above study we found that PCOS can be presented in different ways in women of reproductive age. Prevalence of PCOS is more in young women of reproductive age and is marked by hyperinsulinaemia and hyperandrogenism. Considering the wide range of clinical presentations, initiative for early diagnosis of PCOD should be taken. Preventive therapy includes modification of lifestyle, having proper diet and exercise which should improve the reproductive, metabolic, cardiovascular risks by halting the disease process and decreasing the morbidity of the patients.
Key words: PCOS, infertile women, diverse spectrum of clinical presentation.

Topic: 1.9 Polycystic ovary syndrome

P050 Hormonal imbalance and body mass index in women with infertility due to polycystic ovary syndrome

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Context
Since obesity exacerbates the hormonal and clinical features of polycystic ovary syndrome (PCOS), and women suffering from PCOS have a higher risk of obesity, it seems logical to assume an involvement of hormonal imbalance in the pathogenesis of PCOS, depending on the constitutional features.

Objective
The aim of the study was to distinguish the features of the metabolism of reproductive hormones in women with infertility due to PCOS, depending on the body mass index (BMI).

Methods. Patients
The study included 100 women aged 25-39 years with infertility due to PCOS (experimental group) and 30 women with infertility due to tubal-peritoneal factor (comparison group).

Interventions
Concentration of hormones of the reproductive system were determined by the immunoenzyme method in all the examined patients. Anthropometric indicators were also measured. Statistical significance of the research results was analysed using "Microsoft Office Excel" and "Statistica" software.

Main outcome measures
It was found that BMI has a weak inverse relationship with the level of follicle-stimulating hormone (FSH), as well as a direct relationship with the concentration of luteinizing hormone (LH), prolactin, estradiol, testosterone and the ratio of LH/FSH.

Results
Analysis of associations between the concentration of sex hormones and BMI showed that the ratio of LH/FSH and the concentration of FSH, prolactin, estradiol and testosterone depended on BMI. The ratio of LH/FSH in women with PCOS and obesity / overweight were significantly higher than those with BMI in the range of 18.5-24.9. Thus, the highest value of the LH/FSH ratio was found in women with the second degree of obesity. The lowest value of FSH was found in women with infertility due to PCOS and the second degree of obesity, and it was lower by 11.76% in women with normal weight. The level of prolactin in the blood of women with infertility due to PCOS and obesity of the first and third degrees was also significantly higher than in the comparison group. The concentration of estradiol in women with PCOS and obesity was higher by 26.06 - 28.55% than in the patients with normal body weight. The concentration of testosterone in women with infertility due to PCOS, who had BMI of more than 25.0 kg/m 2, was also significantly higher.

Conclusions
Obesity exacerbates the hormonal imbalance in women with

Topic: 1.9 Polycystic ovary syndrome

P052 Effects of fish oil omega-3 fatty acid supplementation on cardiometabolic biomarkers in women with polycystic ovary syndrome and metabolic syndrome

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Context

Polycystic ovary syndrome (PCOS), one of the most common endocrinopathies in the general population, affecting 5 to 10% of women of childbearing age. The prevalence of metabolic syndrome (MS) in PCOS is higher than that in general population.

Objective

To evaluate the effects of omega-3 polyunsaturated fatty-acid supplementation on lipid profile, lipid and protein peroxidation, antioxidant defense and inflammation in women with PCOS and MS.

Subjects

Sixty women (29±6 years) were recruited between September 2018 and June 2019. The diagnosis of PCOS was based on Rotterdam criteria and that of MS on the NCEP ATP lll criteria. The prevalence of MS components was (21.6% insulin resistance, 98.33% hypertriglyceridemia, 45% low HDL-C, 56.66% high blood pressure and 100% abdominal obesity). Intervention: All women received nutritional counseling adapted to a Mediterranean diet. They have been asked to consume olive oil for seasonings, whole grains, legumes, vegetables and fruits, combined with daily physical activity. Women with PCOS and MS were randomized into 2 groups; a treated group (T; n=30) received for 6 weeks supplementation with omega-3 fish oil (180mg EPA and 120mg DHA/1g; Doppelherz, Germany) 3g/day, 30 women were assigned to control group (C).

Methods

On serum, we assessed glucose, total cholesterol (TC), triacylglycerols (TG) and high-density lipoprotein cholesterol (HDL-C) by colorimetric method. Low-density lipoprotein cholesterol (LDL-C) by the Friedewald formula. Inflammation status was assessed by CRP according to immunoturbidimetric method (Cobas c 111). For redox status, we analyzed thiobarbituric acid-reactive substances (TBARS) (Quintanilha et al., 1982), carbonyls (Levine et al., 1990), thiols (Sedlak & Lindsay, 1968) and activity of; superoxide dismutase (SOD) (Marklund & Marklund, 1974) and catalase (Goth., 1991).

Results

After 6 weeks of intervention, in (T) compared to (C) there was a significant decrease ($p<0.05$) in fasting blood glucose levels. TG, TC, HDL-C and LDL-C were unchanged. No significant decrease was observed for CRP concentrations. TBARS and carbonyls amounts were unchanged, however, a significant increase by 7% in thiols and by 12% in SOD activity was observed ($p < 0.05$) in (T) compared to (C). Catalase activity was similar.

Conclusion

Omega 3 supplementation improves hyperglycemia and antioxidant defense in patients with SOPK and MS and may lead to decreased rates of cardiovascular complications.

Topic: 1.9 Polycystic ovary syndrome

P053 Association between insulin resistance and ovarian morphology in women with PCOS

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Context
Insulin resistance (IR) is likely involved in the promotion of Polycystic Ovary Syndrome (PCOS) reproductive phenotype and may mediate the ovarian morphology (OM).

Objectives
Evaluation of the association between OM and IR in women with PCOS.

Methods
OM was assessed by trans-vaginal ultrasound and IR was measured by HOMA-IR. Metabolic parameters (HOMA-IR, glycemic status, waist circumference, acanthosis nigricans) were compared with ovarian volume (OV) and ovarian follicle number (OFN) separately.

Patients
Newly diagnosed 100 PCOS patients according to Rotterdam criteria were included.

Interventions
No intervention. Cross-sectional observational study.

Main outcome measures
OV, OFN, HOMA-IR

Results
82 subjects had IR (fasting insulin ≥12 μIU/ml, HOMA-IR ≥2.6), 76 subjects had increased OV >10 cc and 70% had OFN ≥12 in either or both ovaries. IR was not significantly associated with OV or OFN.

Conclusions
OV or OFN are not predictive of IR among women with PCOS.

Topic: 1.9 Polycystic ovary syndrome

P054 Non-coding RNAs in polycystic ovary syndrome: a systematic review

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Context
A number of studies indicated that non-coding RNAs (ncRNAs) were involved in occurrence and development of polycystic ovary syndrome (PCOS). Expression levels of ncRNAs in serum, granulosa cells (GCs), follicular fluid (FF) and other tissues are significantly different between PCOS patients and controls. Understanding the role of ncRNAs in PCOS could provide guidance for researcher to further explore the complexity and heterogeneity of PCOS.

Objective
We aimed to summarize current publications regarding various ncRNAs relevant to PCOS.

Methods
We performed a systematic review for all publications in PubMed, Medline, Web of Science and Embase until July 2019, which covered current publications regarding biogenesis of various ncRNAs relevant to PCOS, and then summarize potential role of the involved ncRNAs in pathophysiology of PCOS. Each study was screened by two independent reviewers.

Patients
Studies were considered for inclusion if meet all of the following criteria: 1) original articles containing independent data, 2) reports on ncRNAs and PCOS in human, 3) case–control or cohort studies. Reviews, abstracts, researches based on animal models, articles not written in English or focusing on key drug-regulation ncRNAs in PCOS were excluded.

Intervention (s)
None.

Main outcome measure(s)
We summarized all eligible publications focusing on miRNAs, lncRNAs, circRNAs and siRNAs in PCOS. This review outlines biological function of PCOS-related miRNAs, lncRNAs, circular RNAs and siRNAs from human research. Although there are differences between results of individual studies, the existing literature has proved that dysregulation of ncRNAs is an essential factor in the pathophysiology of PCOS.

Results
A large number of ncRNAs with altered levels were observed in plasma, serum, follicular fluids, granulosa cells or other issues from PCOS patients compared with control group. The aberrant ncRNAs expression might lead to aberrant steroidogenesis, adipocyte dysfunction, increased ovarian cell proliferation and/or apoptosis, which help to explain the pathophysiology of PCOS.

Conclusions
Current researches showed that microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) and small interfering RNAs (siRNAs) may play an important role in abnormal steroidogenesis, adipocyte dysfunction, increased ovarian cell proliferation and/or apoptosis in the pathogenesis of PCOS.

Topic: 1.9 Polycystic ovary syndrome

P055 Evaluation of polycystic ovarian syndrome among young females attending a tertiary care centre

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Objectives
To find out prevalence of polycystic ovarian syndrome among young girls. To describe the clinical, anthropometric, lifestyle, menstrual, biochemical/Ultrasound and hormonal profile among young girls.

Methods
Study was conducted in VPIMS, Lucknow, India among 1000 girls of age (15-25 yrs). Married females were excluded. Data was recorded on a semi-structured proforma. Clinical and anthropometric profile was noted. Menstrual irregularities were classified according to flow, volume, regularity and frequency using FIGO criteria. Hirsutism noted according to Ferriman-Gallwey score. Biochemical/Ultrasound and hormonal profile were noted.

Results
The prevalence of PCOS was 29.4% by Rotterdam criteria. Mean age of PCOS was 18.54 yrs. Among PCOS diagnosed majority had BMI in normal range 70%, 11% were overweight and 19% obese. Oligomenorrhea in 91%, hirsutism in 58.4%, hypertension in 42%, hyperglycemia in 21.3%. Oligomenorrhea and polycystic ovaries on USG among 51.2%. Obese girls with PCOS had sedentary lifestyle, were more hirsute, hypertensive, high blood sugar levels and dyslipidemia compared with non obese PCOS girls.

Conclusion
PCOS is one of the most common emerging reproductive endocrinological disorder among young females. Young age females at risk of metabolic syndrome should be screened. It is important to prevent early and late sequel of the syndrome. Life style modification and early diagnosis and treatment is need of hour.

Topic: 1.9 Polycystic ovary syndrome

P056 Effect of vitamin D supplementation on psychological dysfunction in vitamin D deficient polycystic ovary syndrome women

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Contex

Polycystic ovary syndrome (PCOS) is associated with anovulation, hyperandrogism, and metabolic disturbances (insulin resistance, obesity, and diabetes). A high risk of mood disorders and stress is common in PCOS. A high prevalence of vitamin D deficiency has been shown in PCOS. Vitamin D plays a role in ovulation and metabolic changes and may be associated with depression.

Objective

To assess the effect of vitamin D supplementation on the quality of life and depression symptoms in vitamin D deficient young women with PCOS.

Methods

Prospective, longitudinal study. Statistical analysis included Chi-square tests, Pearson's correlation, t-Student test. Patients. 38 vitamin D deficient women aged 19-33 with PCOS (according to Rotterdam's criteria) with different symptoms of mental distress (emotional lability, low mood, depression, disturbed sleep) were evaluated. Serum 25 OH vitamin D levels were assessed. A validated Hamilton anxiety rating scale (HAMR) allowed assessment of depressive symptoms (score 0-17 mild, 18-24 moderate, more than 25 severe), and SF 36 scale Physical Functioning and Mental Health was used for assessment of the quality of life. All patients were administered Ultra-D (2000 IU vitamin D per day) within 8 weeks.

Results

The mean baseline level of 25OHD was 17,3±6,1 ng/ml. 29 patients (76%) met HAMR criteria for mild depression and 9 patients (14%) met HAMR criteria for moderate to severe depression. Using the SF scale, it was found that the baselines of Physical activity and Mental health were 54,4±6,1 (95% CI 50,4-56,5) and 62,3±6,9 (95% CI 55,7-66,8), respectively. After 8 weeks of consumption, 25 OHD level raised by 48,8±8,3 ng/ml ($p<0.001$). Only 7 patients (18%) met HAMR criteria for mild depression and no patients met HAMR criteria for moderate to severe depression ($p<0.01$). A significant difference was found in Physical functioning ($p<0.001$) and Mental health ($p<0.01$) - 66,2±7,0 (95% CI 61,1-69,9) and 71,2±8,9 (95% CI 69,7-73,2), respectively.

Conclusions

Regarding the results of the study, vitamin D supplementation significantly improves depression symptoms, decreasing the prevalence of depression and anxiety and the quality of life (physical functioning and mental health) in vitamin D deficient women with PCOS.

Topic: 1.9 Polycystic ovary syndrome

P057 Effect of medical therapy of polycystic ovary syndrome in young adolescent girls

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Contex
Polycystic ovary syndrome (PCOS) is the most common reason for chronic anovulation in young girls in juvenile period. Effect of hyperandrogenism and metabolic disturbances on reproductive development are relevant. Identification and medical correction of PCOS in young adolescent girls may improve the results of medical care and reproductive health in future life.

Objective
To evaluate the effect of medical therapy on hyperandrogenism (biochemical and clinical) and ovulatory function in young girls with classic phenotype of PCOS.

Methods
Prospective, longitudinal study. Statistical analysis included Chi-square tests, Pearson's correlation.

Patients
35 girls in 13-18 years old with classic phenotype of PCOS (according to Rotterdam's criteria) and 30 healthy young girls with normal menstrual function were evaluated. In the PCOS group in association with insulinresistance (n=14), COCs (0,02 mg ethynilestradiol + 3 mg drospirenone) and metformine (500 mg daily) were administered for 6 months.

Main outcomes measurements
Ferriman Gallwey Scale, total testosterone, index of free testosterone (IFT), luteal hormone (LH), folliculostimulating hormone (FSH), sex hormone binding globulin (SHBG), body weight index (BMI), estradiol, insulin resistance (IR-HOMA).

Results
Patients in two groups of equal age were compared (16,1±0,8 y.o. in PCOS vs 16,1±0,8 y.o. in control group) and duration of menstrual function (3,6±1,1 years in PCOS vs 3,8±0,8 years in control group). An inverted puberty was revealed in 34,2% of PCOS girls. In comparison with the control group, in PCOS were revealed higher Ferriman Gallwey's index (19.2±0.43), LH (10,28±0,93 IU/L vs 6,11±0,62 IU/L, $p<0.01$) and LH/FSH ratio (2,1±0.13 vs 1,2±0,13 IU/L, $p<0.01$), decrease in SHBG level (46,7±3,1 nmol/L vs 97,44±10,01 nmol/L, $p<0.01$) and estradiol level (49,1±2,6 pg/ml vs 59,32±9,07 pg/mL, $p<0.05$). Overweight and obesity were revealed in 17,1% girls with PCOS, and insulin resistance in 34%. IR-HOMA was positively correlated with total testosterone level ($r=0.26$, $p<0.01$). After combined treatment in PCOS group, following intervention, biochemical hyperandrogenism reduced in 94,2%, androgenic dermopathy in 85%, insulin resistance in 51,4%. In three months after combined therapy ovulatory menstrual cycle was normalized in 94,2% girls.

Conclusions
Combined medical therapy in young girls with classic phenotype of PCOS and insulin resistance improves hormonal and clinical parameters of hyperandrogenism and normalize ovarian function.

Topic: 1.9 Polycystic ovary syndrome

P058 A study on the relationship between the six sex hormones of mature follicle and pregnancy in patients with polycystic ovary syndrome

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Objectives

To observe the relationship between six sex hormones of mature follicle in ovulation induction cycle and pregnancy in patients with polycystic ovary syndrome (PCOS).

Methods

A total of 200 patients with PCOS who were want to get pregnant, coming form March 2019 to November 2019 to the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, signed voluntarily informed consent to participate in this research project. The patients were divided into normal weight group and overweight group according to whether their body mass index (BMI) was lower or greater than 25, and according to whether the patients are pregnant after ovulation induction treatment, they are divided into pregnant group and non pregnant group. The differences of age, waist circumference, hip circumference and six sex hormones include follicle-stimulating hormone(FSH), luteinizing hormone(LH), estradiol(E2), progesterone(P), prolactin(PRL) and testoaterone(T) in ovulatory cycle were compared.

Results

There was no significant difference in age, waist circumference, hip circumference, FSH, P, PRL between the pregnant group and the non-pregnant group ($p>0.05$). In patients with normal weight, the levels of LH and E2 in the pregnancy group were significantly higher than those in the non-pregnancy group, with significant difference($p<0.05$). There was no significant difference in the T level between the pregnancy group and the non-pregnancy group($p>0.05$). In the overweight patients, there was no significant difference in LH and E2 levels between the pregnancy group and the non-pregnancy group($p> 0.05$), and the T level in the pregnancy group was significantly higher than that in the non-pregnancy group ($p< 0.05$).

Conclusions

The elevation of LH and E2 levels in mature follicles during ovulation induction cycle in patients with polycystic ovary syndrome(PCOS) has positive effects on the chance to get a pregnancy, which can play a guiding role in the successful pregnancy of ovulation induction treatment to a certain extent.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals' Ascent Plan, code: DFL20181401

Topic: 1.9 Polycystic ovary syndrome

P059 Methylation pattern of the promoter region of POMC and FTO genes in patients with polycystic ovary syndrome: a case-control study

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Context

Women with Polycystic Ovary Syndrome (PCOS) have higher prevalence of overweight (RR: 1.95), obesity (RR:2.77) and central obesity (RR: 1.73). The etiology for this higher prevalence is multifactorial. Studies suggest an epigenetic mechanisms, as genic methylation, to explain this phenotype. In this context, genes related to appetite, satiety and metabolism, as POMC (pro-opiomelanocortin gene) and FTO (fat and obesity associated gene), take on a relevant role. Methylation patterns of POMC and FTO genes have already been associated to obesity in some clinical scenarios, but never specifically related to PCOS.

Objective

To evaluate the methylation pattern of the promoter region of POMC and FTO genes in patients with PCOS and controls, as well as relate these patterns to BMI.

Methods and Patients

It is a case-control study, with 38 PCOS and 35 control patients, paired by age and body mass index (BMI). For genic methylation analysis the DNA was extracted from peripheral blood leucocytes and modified by sodium bisulfite, then amplified by real time PCR. The percentage of methylation was determined by a semi-quantitative method using the High Resolution Melting curve method. The results were analyzed by grouping the samples according to the following methylation patterns: hypomethylated (0-20%), partially methylated (50%) and hypermethylated (≥80%).

Intervention

Observational study.

Main outcome measure

Methylation pattern of a promotive region of the POMC and FTO genes in PCOS patients and controls.

Results

Groups had similar age and BMI. There was no difference between the two groups in relation to the methylation pattern of the studied fragment of the promoter region of the genes POMC and FTO. For the POMC gene there was a predominance of hypermethylation (in 90% of the samples) in both groups. On the contrary 90% of samples in both groups were hypomethylated for FTO gene. Afterwards the two groups were subdivided according to BMI categories in normal weight (BMI ≤24.9Kg/m^2) and weight excess (BMI ≥25.0Kg/m^2). There was also no difference in the methylation pattern between the four subgroups, despite the BMI.

Conclusions

Despite the similarity found in the methylation pattern of the studied regions, there might be differences in other regions of the promoter genes or even in the same regions in other tissues in patients with PCOS.

Topic: 1.9 Polycystic ovary syndrome

P060 Metabolic, imaging and hormonal parameters correlate with polycystic ovary syndrome

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Polycystic Ovary Syndrome (POCS) is a very common disorder whose diagnosis definition is still not established. The aim of the study was to evaluate the correlation between endocrine and metabolic parameters and ovarian morphology by imaging.

Methods

This is an observational, case/control, monocentric study performed at Obstetrics and Gynecology Unit at AOU Careggi, Florence, Italy. Seventy (70) women aged between 18-30 years old with POCS diagnosis (case group) according to Rotterdam criteria (2003) were selected and compared with 60 normal menstrual cycled women (control group) of the same age. All patients were evaluated through a multidisciplinary approach which included: clinical history, transvaginal ultrasound ovarian examination, hormonal profile and metabolic evaluation. Fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), fasting blood glucose, 17 hydroxyprogesterone (17OHP), LH/FSH ratio, Sex Hormone Binding Globulin (SHBG) and ovarian volume (OV) were measured in POCS patients and controls. In group of POCS patients (n = 38), Serum Anti-Müllerian Hormone (AMH) was measured.

Results

The OV mean (MOV) was 12.52 ml +/- 2.2 in POCS, 7.37 ml +/- 3.5 in controls our study showed a correlation between OV and fasting insulin, considering OV as a continuous variable. Instead, there was a significant correlation ($p<0.05$) between OV (considered as dichotomous variable), and LH/FSH ratio, fasting insulin, HOMA index. The relation of OV with the other variables was not statistically significant. There was a linear correlation and regression between AMH and androstenedione ($p=0.006$ and $p=0.002$, respectively).

Conclusions

Our study showed that in POCS women, the OV correlated with fasting insulin, HOMA index and LH/FSH ratio; furthermore, a correlation and regression between AMH and androstenedione was observed.

Topic: 1.9 Polycystic ovary syndrome

P061 Long-term effects of spironolactone treatment in PCOS patients

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Background

Hyperandrogenic skin symptoms, such as hirsutism, acne and alopecia, affect approximately 10–20% of women of reproductive age, reducing quality of life and causing psychological impairment. Polycystic ovary syndrome (PCOS) is the most frequent cause of hyperandrogenic disorders. Spironolactone (SP) is the most commonly used antiandrogen, especially in women who are not sexually active or with contraindications for hormonal contraceptives. Several evidences support its efficacy similarly to other antiandrogens and oral contraceptives, however only few studies have evaluated its long-term effects, especially the suspension. The aim of the study was to assess the long-term effects and safety of SP in PCOS patients with hyperandrogenic skin disorders and the time of persistence of the effects after its withdrawal.

Material and Methods

Retrospective analysis of 63 PCOS women, diagnosed according with Rotterdam criteria, affected by hyperandrogenic skin symptoms, treated with SP for at least 6 months as first-line treatment. Main outcomes included improvement and the persistence of the effects after withdrawal of spironolactone. Hyperandrogenic symptoms were quantified by modified Ferriman-Gallwey score for hirsutism, by comprehensive acne severity scale for acne and by Ludwig scale for alopecia. All data were prospectively collected by the same physicians.

Results

After a mean time of treatment of 25.3 months, all patients reported a significant improvement in all hyperandrogenic skin disorders, even if 5 patients were not satisfied. 20 patients complained relapse of hyperandrogenic skin symptoms, with an average time of 18±14.4 months after withdrawal SP. Patients with persistent remission and those with a relapse of symptoms did not present any significant differences of baseline and clinic and biochemical parameters; only ovulatory PCOS patients were treated for a shorter time and reported earlier relapse compared with classic PCOS patients. The therapy was well tolerated and the most frequent side-effect was intermenstrual bleeding in 68.2% of cases, mainly with classic PCOS phenotype.

Conclusions

SP is an effective and safe treatment for both hirsutism, acne and alopecia, showing persistent effects even several months after its withdrawal in more than half of treated patients. This effect seems to be independent from baseline and final clinical and biochemical features of patients.

Topic: 1.9 Polycystic ovary syndrome

P062 Comprehensive assessment of the glycosaminoglycans effect on the hemostatic system in patients with polycystic ovary syndrome

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Context
Polycystic ovary syndrome (PCOS) remains one of the most common conditions among the reproductive-aged women, having a significant impact on various body systems. Endothelial dysfunction plays an important role in the pathogenesis of polycystic ovary syndrome, which increases the risk of cardiovascular complications. Administration of drugs containing glycosaminoglycans, may prevent the complications development of metabolic and vascular profiles due to its angioprotective and profibrinolytic effects.

Objective
To evaluate the effect of drugs containing glycosaminoglycans, which has a high endothelial receptivity, on the hemostasis in patients with polycystic ovary syndrome.

Patients
The study included 60 patients with the diagnosis of polycystic ovary syndrome.

Methods
The patients were divided into 2 groups according to the body mass index: patients with normal body weight (n=30) and patients with obesity (n=30) in order to comparatively assess the hemostatic parameters and analyze the effectiveness of the vasoprotective drug usage. The control group consisted of 30 healthy patients with normal body weight.
Interventions. In order to estimate the hemostatic system conditions and presence of concomitant pathologies the study included conducting physical examination, assessment of clinical features of PCOS, menstrual cycle analysis, ultrasound examination of pelvic floor organs, blood test with determination of hormonal profile.

Main outcome measures
During the study all patients underwent a comprehensive assessment of the main parameters of hemostatic system.

Results
The results of the study indicate a significant impact of endothelial dysfunction on the hemostatic system in patients with PCOS regardless of body weight. The application of drugs composed of glycosaminoglycans has proven its feasibility and effectiveness as an angioprotective medication in cases of PCOS. In the presence of metabolic disorders the therapeutic effect is more significant, which is confirmed by the pronounced dynamics of platelet count, thrombin time, fibrinogen and homocysteine levels.

Conclusion
Taking into consideration the development of endothelial dysfunction in patients with polycystic ovary syndrome, the use of drugs composed of glycosaminoglycans reduces the risk of cardiovascular complications. It enables to improve the results of pregravid preparation and increase the possibility of favorable perinatal outcomes in this cohort of patients.

Topic: 1.9 Polycystic ovary syndrome

P063 The frequency of diabetes mellitus during pregnancy of patients with PCOS in Primorsky Krai

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Contex
Identification of gestational and manifest diabetes mellitus during pregnancy of women who bears PCOS with different phenotypes

Objective
The study included 135 pregnant women from 24 to 37 years old with PCOS who had a first pregnancy that ended in delivery. Phenotype A of 75 women, with phenotype C of 60 women, phenotype B and D were not detected, the control group consisted of 45 women without PCOS, but who were obese before pregnancy.

Methods
Before pregnancy, all patients underwent anthropometric indicators: BMI 27.33 ± 4.36 kg \ m^2, FR 88.3 ± 4.0 cm. Before pregnancy, there were no disorders of carbohydrate metabolism. During pregnancy, a study was conducted of fasting glucose levels, glycated hemoglobin (HBA1c) was performed every 4 weeks, oral glucose tolerance test in each trimester of pregnancy up to 28 weeks. The tolerance test was evaluated according to the criteria of 2012.

Results
Of women with phenotype A, gestational diabetes mellitus (GDM) was detected of 12 women (16%). 7 women were identified on the basis of an increase in fasting glucose, of 5 women using an oral glucose tolerance test. Manifested diabetes mellitus was revealed to two women, requiring insulin therapy. Of women with phenotype C, (GDM) was detected of 6 women (10%),4 women were identified on the basis of an increase in fasting glucose, of 2 women using an oral glucose tolerance test. In the control group, 3 patients (6.6%) without PCOS was also diagnosed with GDM. To all women with GDM are diet and blood glucose self-monitoring were recommended. All women have an increase in body weight per pregnancy of 10-12 kg.

Conclusions
PCOS is one of the reasons for the risk of gestational and manifest diabetes mellitus. Revealing diabetes is more common in patients with phenotype A, conducting a glucose tolerance test, fasting glucose, HBA1c at different stages of pregnancy and the joint work of gynecologists and endocrinologists can reduce the risk of GDM, allows timely initiation of therapy, reduces the risk of fetal, obstetric complications.

Topic: 1.9 Polycystic ovary syndrome

P064 Study on the changes of hormone levels in early pregnancy of polycystic ovary syndrome and its influence on the outcome of early pregnancy

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Objective

Polycystic ovary syndrome (PCOS) patients have a higher rate of early pregnancy loss. The purpose of this study is to study the changes of hormone levels in early pregnancy in PCOS patients and the impact on pregnancy outcome.

Methods

Within a prospective, case-control study outpatients with pregnancy coming to the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, China, from March to September 2019 were collected and divided into the PCOS group (Study Group) (n = 55) and healthy control group (n = 32). The outcome of early pregnancy (within 12 weeks), hormone levels (Chorionic gonadotropin (β-hCG), progesterone(Po), Estradiol (E2), Prolactin (PRL), thyroid stimulating hormone(TSH), Total testosterone (TT), Free testosterone (FT), Bioactive testosterone (BioT), Sex hormone binding protein (SHGB)) after 8 weeks and 9-12 weeks were recorded.

Results

In the study group TT, FT and BioT were higher than those in the control group ($P < 0.05$), while β-hCG, Po, TSH and PRL did not show significant differences. There were no significant differences in TT, FT, BioT between early pregnancy loss and clinical pregnancy in PCOS patients within 8 weeks ($P > 0.05$), while FT, BioT in 9-12 weeks gestation were significantly higher than those in the clinical pregnancy group ($P < 0.05$).

Conclusion

The testosterone levels of PCOS patients show an increasing trend during pregnancy, and increased values of testosterone at 9-12 weeks are important for the evaluation of the outcome of early pregnancy.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals'Ascent Plan, code: DFL20181401

Topic: 1.9 Polycystic ovary syndrome

P065 Health-related quality of life assessment in chinese women with PCOS using Chi-PCOSQ

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Context
Polycystic ovary syndrome (PCOS) has clinical implications for long-term health that may lead to decreased quality of life (QoL). Limited data exist on QoL in Chinese women with PCOS.

Objective
To assess QoL in Chinese women with PCOS.

Methods
Women were interviewed, general questionnaire including demographic data /clinical features was obtained and QoL was assessed by short-form 36 (SF-36) and Chinese version of PCOS questionnaire (Chi-PCOSQ).

Patient(s)
36 Chinese women aged 18-35 with PCOS diagnosed by the 2003 Rotterdam criteria (PCOS group) and 28 age-matched healthy controls (Control group).

Intervention(s)
Cross-sectional study.

Main outcome measure(s)
The SF-36 questionnaire and Chi-PCOSQ.

Results
PCOS women had higher levels of BMI (25.58±5.13 vs 21.65±2.88) and WHR (0.85±0.07 vs 0.77±0.37) than controls ($p<0.001$, respectively). These women had an increased free androgen index and over 50% of them had Ferii-Gail score ≥6. Compared to controls, QoL of PCOS women assessed by the SF-36 tended to be poorer in domains of physical function, bodily pain and physiological role, however their QoL were obviously poorer in domains of vitality, social function and mental health ($p<0.05$, respectively). The PCOS women was further divided into PCOS-lean (BMI<25) and PCOS-obese (BMI≥25) groups. Compared to controls, QoL was poorer both in PCOS-lean and PCOS-obese women in vitality, social function and mental health domain ($p<0.05$, respectively), however QoL was poorer in domains of physical function, physiological role and bodily pain only in the PCOS-obese women ($p<0.05$, respectively). QoL scores in Chi-PCOSQ domains including emotion, body hair, weight, infertility and menses were lower in PCOS women than in controls ($p<0.001$, respectively). The weight domain score was the lowest, followed by infertility, emotion, menses and body hair. Moreover, QoL score was lower both in PCOS-lean and PCOS-obese women in all Chi-PCOSQ domains compared to controls ($p<0.001$, respectively). In addition, WHR was negatively correlated with the domain score in physical function, physiological role, bodily pain ($p<0.05$, respectively), and emotion, body hair, weight, infertility and menses ($p<0.01$, respectively). Ferii-Gail score and testosterone level were negatively correlated with the body hair domain score ($p<0.05$, 0.001).

Conclusions
Chinese women with PCOS have impaired QoL. The weight is first factor that influences QoL in Chines women with PCOS.

Topic: 1.10 Insulin resistance

P066 Frequency of insulin resistance in polycystic ovary syndrome by homeostatic model assessment (HOMA), endocrinology gynecological Maternity Hospital Our Lady of Altagracia

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Type of study

An observational study was conducted. The sample consisted of 76 patients with POS.

Goals

Show that the frequency of insulin resistance in women with POS is high.

Results

The 67.1% showed insulin resistance. 37.2% was the daughter of a diabetic mother. The major phenotypes of the POS A and B are 33.3 and 39.2%.

19.6% percent of the patients presented basal glycemia between 100-126 mg / dl. 4% are diabetic. 41.1% entering the range being pre hypertensive and 23.4% is hypertensive. 17.6% was normo weights; the rest with some degree of obesity. 61.8% of patients had increased the diameter of the waist circumference.

44.1% of patients presented Simple endometrial hyperplasia.

98% received as therapeutic as metformin, 56% of the patients received 850mg, 42% received 850 mg twice a day, the remaining insulin.

Conclusions

The age was between 15-39 years (they were adolescents and young adults), with diseases such as obesity, insulin resistance, hyperlipidemia and hypertension presents 23.4% (stage I or II).

POS patients with gynecological complications like metabolic present. Partnering with endometrial cancer. The ACOOG says that chronic anovulation, obesity, hyperinsulinemia and low level of HSBG, are all associated with endometrial cancer

Recommendations

Patients with POS require an early and accurate diagnosis. According to the principles of Lamarckian medicine ranges from epigenetic changes and intrauterine origin of the disease of the adult daughters of mothers with hyperglycemia, hyperandrogenism, small for gestational or great age, since the evidence-based medicine has been shown these stored data direct and proportional relationship to the development of polycystic ovary syndrome, and can even syndrome appear in early stages of life as premenarquia. When receiving a patient in our practice based on this should include prenatal history, complications from their mothers and the birth weight

Many of the present complications, require multidisciplinary follow-up so we recommend if necessary manage patients with other specialists. So we avoid adding morbidity to the patient not be met on time. In general we should counsel patients that alterations in the menstrual cycle are not normal, that reflect the organic or systemic changes therefore must seek help early. A time to assess patients demos include in our physical anthropometric measurements.

Topic: 1.11 Obesity, metabolic syndrome

P067 Association between bariatric surgery and contraceptive use, menstruation, and clinical presentation of hyperandrogenism – a case-control study

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Context

Bariatric surgery (BS) procedures are considered to be the most decisive and effective methods of obesity treatment. Their impact affects various aspects of life and numerous studies indicate a significant effect on the female reproductive system.

Objective

To assess the long-term association between BS, contraceptive patterns, menstrual regularity, and clinical features of hyperandrogenism.

Methods

It was a cross-sectional survey-based study of patients who underwent BS. Patients answered questions considering contraceptive patterns, menstrual regularity and hyperandrogenism clinical features before surgery and during the last year.

Patients

The study population included 624 women who underwent BS between January 2006 and December 2017 at the Military Medical Institute, Warsaw, Poland.

Intervention

Patients underwent either a Roux-en-Y gastric bypass (RYGB; 26.3%), sleeve gastrectomy (SG; 64.6%) or both of them.

Main outcome measures

The prevalence of irregular, long (>7days) menstruations, estrogen-based contraception use, hyperandrogenism clinical features (acne, hirsutism) during year before BS and during the last year was established and correlated with surgical and demographic parameters.

Results

There was observed a significant increase in the number of patients who had regular menstrual pattern after the BS (69.6% vs. 60.2%; p<.001) and a decrease in those who experienced long bleedings after BS (11.7% before BS vs. 7.7% after; p<.02). No significant difference in the prevalence of acne (28.3% vs. 25.3%; p<.24) and hirsutism (33.1% vs. 33.3%; p<.95) was observed before and after BS. There were no significant differences in terms of estrogen-based contraception before and after BS (13.5% vs. 13.1%; p<.085).

Conclusions

Bariatric surgery seems to have a positive effect on menstruations. BS does not seem to have any impact on the clinical features of hyperandrogenism. The relatively high use of estrogen-based contraception among patients who experience obesity is alarming.

Topic: 1.11 Obesity, metabolic syndrome

P068 Effects of alpha-lipoic acid and myoinositol supplementation on the oocyte environment of obese infertile women

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Introduction

Obesity is characterized by increased inflammation and oxidative stress, resulting in adverse effects on women reproductive potential.

Antioxidant supplementation may exert a positive effect on the obese ovarian environment. Indeed, we preliminarily observed a reduction of mitochondrial (mt) DNA content, a marker of oxidative stress, in granulosa cells of obese infertile women supplemented with Sinopol® (Laborest SpA), composed by alpha-lipoic acid (ALA) 800 mg, myoinositol (MYO) 2 g, folic acid (FA) 400 ug. Here we analyzed Total Antioxidant Capacity (TAC) in follicular fluid and mtDNA levels in granulosa cells, in a larger population of infertile women undergoing *in vitro* fertilization (IVF).

Methods

19 normal weight (NW) and 24 obese (OB) infertile women were enrolled in our IVF center. All women were provided with FA and among them 15 OB (OB-SIN) were also supplemented with ALA and MYO, for 2 months before ovarian stimulation.

Follicular fluid (FF) and granulosa cells (GC) were collected after oocyte retrieval. TAC was measured in FF by enzymatic assay, mtDNA levels evaluated in GC by Real-time PCR.

Results were compared by ANOVA and correlations assessed by Pearson's correlation (SPSS; IBM).

Results

OB groups had similar BMI (OB patients supplemented with only folic acid (OB-F): 30.2 ± 0.7; OB-SIN: 32.7 ± 1.1 kg/m^2). Women age was similar in all groups (NW: 36.7 ± 0.6; OB-F: 37.6 ± 1.7; OB-SIN: 35.9 ± 1.1 years).

Among OB women, antioxidant capacity was significantly higher in OB-SIN than in OB-F.

mtDNA levels showed an opposite trend, being decreased in OB-SIN and increased in OB-F compared to NW, though not reaching statistical significance. mtDNA levels were significantly and inversely correlated with the number of total oocytes and metaphase II (mature) oocytes.

Pregnancy rate was similar in NW (36.8%) and OB-SIN (33.3%) women, while it was lower in OB-F patients (11.1%).

Conclusion

We analyzed molecular markers in granulosa cells and follicular fluid as indicators of oocytes oxidative state. Our results suggest that supplementation with a compound of ALA -a natural antioxidant, cofactor in the mt respiratory chain- and MYO -an insulin-sensitizer- might increase antioxidant defenses and reduce oxidative stress in the obese ovarian environment, possibly contributing at restoring physiological conditions. This might improve IVF pregnancy rates in obese infertile women.

Topic: 1.11 Obesity, metabolic syndrome

P070 The effect of bariatric surgery on the menopause

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Relevance

The incidence of morbid obesity continues to increase, especially among women of late reproductive and menopausal age. Among the treatment methods, bariatric surgery (BS) showed the best effect on normalizing body weight, cardio-metabolic parameters, as well as improving the course of the menopausal transition.

Goal of research

Assess the effect of bariatric surgery on the menopause.

Materials and methods

A retrospective study of 35 women with morbid obesity, aged from 42 to 55 years, who successfully underwent bariatric surgery (gastric sleeve resection) was conducted. All women were in the period of perimenopause: elevated FSH> 25, monthly irregular, in 26-abnormal uterine bleeding (AUB) with anemia. Metabolic parameters and severity of menopausal syndrome were assessed according to the MRS scale.

Results

12 months after surgery, a decrease in body mass index was observed in 32 (91%) patients, normalization of cardio-metabolic parameters in 30 (86%) patients. The most demonstrative concentrations decreases were found in total cholesterol (from 7.6 ± 0.9 to 5.2 ± 0.7 mmol/L), LDL (3.5 ± 0.2 to 2.8 ± 0.1 mmol/L), triglycerides (1.9 ± 0.06 to 1.4 ± 0.02 mmol/L) and glycated hemoglobin (6.3 ± 0.2 to 5.6 ± 0.1%). At the same time, the severity decrease of the menopausal syndrome was observed from 17.8 ± 2.9 to 9.2 ± 1.7 points. Persistent amenorrhea was established among 29 (83%) women, and a decrease in the volume of menstrual blood loss was noted in 6 (17%) cases.

Conclusion

Elimination of metabolic disorders using bariatric surgery helps to alleviate the menopause in women.

Key words: Menopause, bariatric surgery, menopausal syndrome.

Topic: 1.11 Obesity, metabolic syndrome

P072 Cardiovascular risk factors in women with uterine fibroid after embolization of uterine arteries

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Context
Women with uterine fibroid of the late reproductive and perimenopausal period have an extremely high risk of developing cardiovascular disease (CVD).

Purpose of the study
To analyze cardiovascular risk factors in women with uterine fibroid of the late reproductive and perimenopausal period in the postembolization period.

Methods
A prospective, non-randomized case-control study, including 94 women.

Patients
The study was conducted in the II clinic of the Tashkent Medical Academy for the period 2017 - 2019. 44 women with uterine fibroid were examined after embolization of the uterine arteries and 50 - healthy women.

Interventions
All women underwent standard clinical, laboratory and instrumental studies, the SCORE total cardiovascular risk scale, and bioimpedansometry.

Main outcome measures
The average age of the main group was 49.2±0.8 years. Bioimpedansometry was performed and several parameters calculated indicating a visceral type of obesity.

Results
27.3% of women had an excess of body mass index (BMI) (26.8 ± 0.7 kg / m^2), 17.3% of women had obesity I (33.4 ± 0.8 kg / m^2), and 17.3% - obesity II (37.8 ± 0.9 kg / m^2), in 15.4% - obesity of class III (42.4 ± 1.1 kg / m^2). Assessment of visceral fat in women with uterine fibroid and an excess of BMI showed that 27.3% had 27 points, and women with obesity I, II, and III class had 60 points. Moreover, the metabolic age in women with excess and obesity (77.3%) was 58 years. Muscle mass in women with excess BMI was 3.3% and significantly lower in obesity ($p < 0.001$) (1.4%). The SCORE total cardiovascular risk score was calculated to be low risk in women with fibroid with normal BMI, moderate risk with excess BMI and high risk in women with obesity ($p < 0.001$).

Conclusions
The results show that in women with uterine fibroid of late reproductive and perimenopausal age with an increase in BMI, muscle mass decreases and visceral obesity and the incidence of metabolic syndrome increase, which contributes to an increase in the risk of CVD according to the SCORE total scale.

Topic: 1.11 Obesity, metabolic syndrome

P073 Assessment of endotoxemia in women of reproductive age with obesity and non-alcoholic fatty liver disease associated with menstrual cycle disorders

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Background

Important role in the inflammatory component in obesity and non-alcoholic fatty liver disease (NAFLD) plays bacterial endotoxemia associated with intestinal dysbiosis. The penetration into the blood and liver of endotoxins of pathogenic gut microbiota promotes the synthesis of proinflammatory cytokines activating systemic low-gradient inflammatory process. However, number of studies about the possible role of endotoxins of gram-negative gut microbiota in the pathogenesis of obesity, NAFLD and menstrual disorders in women of reproductive age is still poor.

The purpose

To investigate endotoxemia manifestation in women of reproductive age with obesity, NAFLD and menstrual disorders such as oligomenorrhea, dysmenorrhea, abnormal uterine bleeding.

Methods

We examined 207 people including 64 patients with obesity combined with NAFLD and menstrual disorders (group 1), 64 patients with obesity and menstrual disorders (group 2), 26 patients with NAFLD and menstrual disorders (group 3), 28 patients without obesity and NAFLD but with menstrual disorders (group 4). The control group consisted of 25 healthy individuals. Evaluation of endotoxemia was performed by a spectrum of medium-mass molecules (MMM280) and IgG to LPS of gram-negative gut microbiota in blood serum. The concentration of cytokines (IL- 6, 8 and TNF-α) was determined in serum by ELISA.

Results

Patients of group 1 had the highest levels of IgG to LPS and MMM280, which exceeded the control values 5.8 times and 2.7 times respectively. The results of our studies showed the presence of different severity intestinal dysbiosis in 1-3 groups of examined patients. In patients of 1-3 groups were found increased levels of pro-inflammatory cytokines. We also revealed a significant positive correlation between parameters of edotoxemia and degree of intestinal dysbiosis (r=0.72), between IL- 6, 8 and TNF-α and IgG to LPS (r=0.60) and between IL- 6, 8 and TNF-α and degree of intestinal dysbiosis (r=0.56), which confirms gut dysbiotic disorders impact in systemic endotoxemia and low-grade inflammation in this very patients.

Conclusion

Obtained results indicate the possible role of impaired gut microbiota in the pathogenesis of obesity and NAFLD in this category of patients, which should be taken into account choosing treatment tools for both obesity and targeted menstrual disorders correction.

Topic: 1.11 Obesity, metabolic syndrome

P074 Metabolic Syndrome is associated subclinical hypothyroidism in women with type 2 diabetes mellitus

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Context

To evaluate the possible relationship between metabolic syndrome (MS) and subclinical hypothyroidism (SH) and the response to insulin resistance (IR) in women with type 2 diabetes mellitus (DM). SH in patients with MS may further add to cardiovascular disease risk thereby increasing mortality.

Objective

This study was done to assess thyroid function in woman with type 2 DM and evaluate its relationship with the components of MS.

Methods

SH was defined according to the National Health and Nutrition Examination Survey (NHANES) criteria: high TSH (≥4.12mUI/L) and normal free T4 (0.9-1,9 ng/dL) in subjects without personal history of thyroid disease. MS components were defined according to IDF/AHA/NHLBI/WHF/IAS/IASO-2009 criteria.

Patient(s)

We studied 58 women with type 2 DM duration of 8.3±5.2 years, mean age of the female patients was 44.6±9.4 years, mean value of glycated hemoglobin (HbA1C) - 7.9±1.3%, body mass index (BMI) – 36.9 ±4.6 kg/m^2. All diabetics divided into two groups: (1) the SH group with 28 patients; (2) the euthyroid (EU) group with 30 patients. Among all patients, the most common MS component was low HDL cholesterol (48.9%) and abdominal obesity (64.7%). Physical characteristics and metabolic parameters, function of thyroid gland as well as IR test were compared between these two groups.

Main outcome measure(s)

In the SH group, significantly higher body mass index, serum triglyceride, insulin and glycemic control (the fasting plasma glucose, HbA1C), homeostatic model assessment-insulin resistance (HOMA-IR) and significantly lower serum high-density lipoprotein cholesterol was observed in comparison with those in the EU group ($p<0.05$).

Results

The prevalence of IR (46.4%) and MS (52.8%) in the SH group was significantly higher than that in the EU group ($p < 0.05$).

Conclusions

MS prevalence was higher in SH in women with type 2 DM. In women with MS and SH may have a poorer treatment response to correction of thyroid function associated with IR.

Topic: 1.11 Obesity, metabolic syndrome

P075 Superoxide dismutase in women with diabetes mellitus type 2

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Objective

Oxidative stress is defined as an imbalance between the levels of oxidants and antioxidants in favour of oxidants. The effects of an increased oxidative load are reduced by antioxidant enzymes that convert reactive oxygen species (ROS) to less harmful molecules. The main enzymes participating in the oxidative stress reduction process are superoxide dismutase (SOD), catalase, and glutathione peroxidase. SOD catalyzes the dismutation of superoxide anion into hydrogen peroxide. Recent studies report that oxidative conditions play an important role in the development of metabolic syndrome, obesity, and diabetes mellitus type 2 (DMT2).

Aim

To evaluate the serum levels of SOD in women with newly diagnosed DMT2.

Materials and methods

The study included 20 women with newly diagnosed DMT2 and a control group of 26 clinically healthy women. The fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), HDL-cholesterol (HDL-C) (Olympus AU 480, Beckman Coulter) concentrations were analyzed. Serum Cu/Zn-SOD was determined by ELISA kit (Bio Vendor, Czech Republic). SOD concentrations were measured using "Sirio S microplate reader", SEAC, Italy. Collected data was analyzed using SPSS software, version 17.0. Continuous variables were expressed as mean ± standard error. $P<0.05$ was considered significant.

Results

There were no significant differences in age (33.70±3.14 yrs vs. 30.34±5.76 yrs, $p=0.570$), TC (4.67±0.31 mmol/l vs. 4.47±0.15 mmol/l, $p>0.05$) and LDL-C (3.07±0.24 mmol/l vs. 2.46±0.13 mmol/l, $p=0.09$) between groups. Patients had significantly lower serum HDL-C (1.09±0.15 mmol/l vs 1.68±0.08 mmol/l, $p<0.0001$) and significantly higher TG (1.50±0.22 mmol/l vs 0.70±0.05 mmol/l, $p<0.0001$) and FPG (6.85±0.19 mmol/l vs 4.97±0.08 mmol/l, $p<0.0001$) compared to controls. The SOD levels were found to be lower in women with DMT2 (11.60±1.45 ng/ml vs. 38.95±10.49 ng/ml) compared to controls. The mean difference of SOD between two studied groups is statistically significant (27.35±8.94 ng/ml, $p=0.019$).

Conclusions

Our results indicate that DMT2 is associated with decreased antioxidant reserves and excess oxidative stress. Serum SOD could be an important parameter for determining systemic oxidative stress in women with DMT2.

Keywords: oxidative stress, superoxide dismutase, DMT2

Topic: 1.11 Obesity, metabolic syndrome

P076 Relationship between resistin and clinicopathological characteristics of ovarian cancer patients

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Introduction

Obesity is a risk factor for cardiovascular diseases, diabetes and cancer. The relationship between obesity and numerous cancers, such as endometrial cancer, breast cancer, colon cancer, kidney and pancreatic cancer, has been scientifically proven. However, studies assessing the relationship between ovarian cancer (OC) and obesity remain inconclusive. Some of them confirm the increased risk of OC in obese women, whereas other authors do not show this correlation or even point to higher survival rates among obese patients with OC, which is known as the obesity paradox. Inflammatory processes, which are also induced by substances produced by the adipose tissue, such as adiponectin, resistin, visfatin, leptin, angiotensinogen, angiopoietin-like protein 2, C-reactive protein, tumor necrosis factor α or interleukin-6 and interleukin-18, play a crucial role in the pathogenesis of these diseases. Adipokines, produced and secreted by adi¬pose tissue, exhibit autocrine, paracrine and endocrine effects, thus stimulating the process of carcinogenesis in many different ways.

Objective

The aim of the study was evaluation of resistin in plasma and peritoneal fluid (PF) of patients with ovarian cancer (n=50) in relation to body mass index (BMI) and their clinicopathological characteristics, as well as to verify whether obesity increases the risk of this malignancy.

Methods

The concentration of resistin was determined by enzyme linked immunosorbent assay (ELISA) according to manufacturer's instruction.

Results

The highest concentration of resistin was detected in plasma of OC patients and it was significantly higher (p=0.002) than in the peritoneal fluid. There were no significant differences in restisin level in OC patients depending on FIGO stage, histological grade, cancer type according to Kurman and Shih classification. There were no significant differences in resisin level in relation to BMI of OC patients.

Conclusions

The concentration of resistin is significantly higher in plasma than in the PF of OC patients.
There are no differences in the concentration of resistin in OC patients depending on body mass index.

Topic: 1.11 Obesity, metabolic syndrome

P077 Associations of obesity, C-reactive protein, leptin and chronic endometritis in women of reproductive age from unselected population

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Objectives

To determine the associations of chronic endometritis (CE) with obesity, C-reactive protein, androgens, and leptin in women of reproductive age, recruited from the unselected population.

Study design

Cross-sectional, institution-based study

Methods

We examined 198 women of reproductive age (33,71±5,93 years), recruited during the institution-based, cross-sectional study in 2017-2019. All women wrote informed consent. The exclusion criteria were as follows: a) current pregnancy or lactation; b) history of hysterectomy, bilateral oophorectomy, endometrial ablation, and or uterine artery embolization. All women underwent a standard medical examination, pelvic ultrasound and Pipelle-biopsy with CD 138 detection by immunohistochemistry. Serum samples of all women were analyzed for total testosterone (TT) using Liquid ChromatographyTandem Mass Spectrometry (LC-MS/MS), and DHEAS, leptin, C-reactive protein - by ELISA. The local ethics committee approved the study. Statistical analysis was performed using descriptive statistics, Student t criteria and Spearmen r criteria. The general linear model (GLM) were utilized to model outcomes. Data presented as Mean(SD), p value < 0.05 was considered as statistically significant.

Results

Of 198 examined women, CE was diagnosed in 76 patients (group 1). The diagnosis was based on the number of cells expressing CD138, detected by immunohistochemistry. Women with CE and controls were comparable in terms of socio-demographic data (age, race, education, income, marital status), alcohol intake, smoking, and medical history. The age of menarche, thelarche, adrenarche, frequency of menstrual irregularity and infertility in groups did not differ. At the same time, women with CE had lower pregnancies rate in general and abortions, in particular, while they had a higher frequency of ectopic pregnancies and premature births.

Women with and without CE demonstrated comparable values of total testosterone - 29.5 (21) ng/dl vs 36.2 (26) ng/dl (p=0.06), and DHEAS 196.9(88) pg/ml vs 182.2 (98) pg/ml (p=0.28), accordingly. Serum C-reactive protein and leptin levels were significantly higher in women without CE (with p=0.02 and p=0.01) and positively correlated with BMI, which was lower in patients with CE (25.4 () vs 27.5 (6.3) kg/m^2 in controls). The general linear models (GLM) have shown that the CE (the main outcome), and obesity (as a cofounder) were not associated with DHEAS and TT. At the same time obesity (BMI≥30 kg/m^2), in contrast to CE, demonstrated positive association with C-reactive protein ($\beta = 4.5466$; $p = 0.001$) and leptin ($\beta = 15.540$, $p = 0.001$), whereas leptin was negatively associated with CE (β-5.033, $p = 0.05$).

Conclutions

Our study results have shown that chronic endometritis in women of reproductive age is negatively associated with serum leptin whereas obesity demonstrates positive associations with leptin and C-reactive protein.

Topic: 1.11 Obesity, metabolic syndrome

P078 Disorders of menstrual function among young patients with metabolic syndrome

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According to epidemiological dates in Republic of Moldova the frequency of appearance of metabolical syndrome among women is 34.44 %. The importance of Metabolic syndrome (MS) is that it represents itself the situation of pre-diabetes, in patogenesis of which is situated insulin-resistance. Meantime the SM contribute to dysfunction of menstrual cycles and reproductive function in young women and in case of pregnancy can be complicated by gestational diabetes, preeclampsia and other hard consequences. The aim of study was the evaluation of types of menstrual dysfunctions in young women and the impact of hormonal disorders on the clinic.

Material and methods

The targeted group was women by the age of 19-30 years with manifestation of metabolic syndrome and menstrual dysfunctions. There were performed different types of investigations: clinical (including IBM, TA), biochemical, lipid and glucose profile, hormonal test, USG and statistical methods with RR and CI.

Results

There were obtained dates that proved links between pathogenesis of menstrual and reproductive disorders and metabolic syndrome. It was found that the initially reduced level of E2 and increased E1 in blood plasma in this category of patients causes the increased secretion of GnRH, which, in its turn, increases the sensitivity of receptors to gonadotropic pituitary cells. As a result of the increased production of LH by adenohypophysis increases disrupting the ratio of LH/FSH more than 1 and it leads to hypersecretion of androgens by the ovarian cells with their subsequent hypertrophy. The relative decrease of FSH level leads to a decrease of aromatases secretion, converting androgens to estrogens and a secondary decrease of the level of E2 and anovulation. There is a pathological vicious circle. Clinically, it is manifested by hypomenstrual syndrome, infertility and aggravation of MS severity.

Conclusions

The results of research showed that women who have the Metabolical Syndrome, have the following dysfunctions of menstrual cycle: opsomenoree in 42% cases, spaniomenoree in 20%, opsomenoree and hipermenoree – 13%, spaniomenoree and hipermenoree – 12% and the other. The results of study have proved relatively high level of E1 and androgens among patients with MS, that in its turn support insulin-resistance and lead to development of obesity, diabetes type 2 and hypertonia and maintain the dysfunction of reproductive system.

Topic: 1.11 Obesity, metabolic syndrome

P079 The impact of obesity on the prognosis of hypertensive disorders of pregnancy

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Context

Methods to prevent the development of pathologies due to placental dysfunctions, such as gestational hypertension and preeclampsia are the main approach in order to obtain a better pregnancy prognosis. About half of the cases with gestational hypertension will progress to preeclampsia, the risk of decompensation being inversely proportional to the gestational age of onset of gestational hypertension.

Objective

The mechanism by which obesity is an important risk factor for preeclampsia is dictated by the multiple common characteristics of both obesity and preeclampsia, namely: hyperinsulinism, increased insulin resistance, increased leptin, TNF-α, IL-6 and C-reactive protein with altered lipid profile and decreased flow-mediated vasodilation.

Patients and Methods

During five years (2015-2019) of study were analyzed the cases of pregnancy and lousiness complicated with pathology due to placental dysfunction by collecting data from the department of medical statistics of the Bucharest Emergency University Hospital. The case groups included the control group 1, respectively the general population, the group 2, patients with preexisting pregnancy hypertension, the group 3 patients with gestational hypertension, the group 4 included patients with moderate preeclampsia, the group 5 included patients with severe preeclampsia, and the group 6 included patients with eclampsia.

Main outcome measures

Significant results were obtained by comparing the control group with the groups of patients with gestational hypertension, moderate preeclampsia and severe preeclampsia for the incidence of obesity, which appears with a significantly increased incidence in patients with gestational hypertension and mild preeclampsia.

Results

Also, we obtained a mean effect of obesity compared between groups, which significantly differentiate the risk for mild preeclampsia. Following the calculation of the worsening risk, we obtained the fact that obese patients have an increased risk of having moderate preeclampsia, following gestational hypertension and finally severe preeclampsia.

Conclusion

In conclusion, obesity is a risk factor with a significant impact of the development of the mild preeclampsia and not of the severe preeclampsia compared to the general population. The patients with pregnancy-induced hypertension who are overweight have an increased risk of progression to the mild preeclampsia and are protected from developing severe preeclampsia.

Topic: 1.11 Obesity, metabolic syndrome

P079b Vitamin-mineral supplementation as a new therapeutic approach to metabolic syndrome: a case report

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Objective

Metabolic syndrome is a cluster of symptoms that include abdominal (central) obesity, high blood pressure, low HDL cholesterol, elevated triglycerides, elevated morning glycemia. Modern research shows that a new therapeutic approach (combination of standard metformin therapies with vitamin-mineral supplementation) can make patients' symptoms improve faster.

Patient

The patient (female, 29) was admitted to the clinic to be prescribed diet therapy. Anamnestic allegations: insulin resistance, hypertension, frequent urticaria, joint pain, constipation, heartburn. Menstrual cycles neat. He denies obesity in the family. The therapy includes: metformin 1000 mg 2x1, fosinopril 20 mg, amlodipine 10 mg, propranolol 40 mg. On examination: BMI 45.9, blood pressure 125/95 mmHg, waist circumference 130 cm, present hairiness on the face and breast areolas. In the laboratory: Matsuda index 1.2, HDL cholesterol 1.54 mmol/l, triglycerides 1.78 mmol/l. HbA1c 7.6%, prolactin 766.5 mIU/ml, Vitamin D 13 nmol/l, parathormone 120.5 pg/ml, elevated A-TPO (104 IU/ml), gonadotropin, sex hormone and adrenal hormone levels are normal. Ultrasound findings of the abdomen, thyroid gland, breasts and small pelvis are normal. NMR of the sella turcica shows an orderly finding.

Interventions

The patient starts a low-carb diet according to ESPEN recommendations for the diet of patients with metabolic syndrome (35-40% fat, 40-45% carbohydrates, 20% protein) with an emphasis on the intake of complex carbohydrates and fiber, with a 30-minute walk 3 times a week. Add to therapy: Vit. D 2000 IU 1x1, L-selenomethionine 100 mcg 1x1, Mio-inositol 2000 mcg 2x1, R α lipoic acid 200 mg 1x1, chromium picolinate 200 mcg 1x1.

Main outcome measures

After 6 months, the patient lost 25 kilograms, one antihypertensive was excluded, Matsuda index 2.4, lipidogram normal, HbA1c 5.5%, prolactin at three times within the reference values, vitamin D 85 nmol/l, parathyroid hormone 65.8 pg/ml, A-TPO values in significant decline (55 IU/ml). Ultrasound finding of the thyroid gland stationary.

Conclusion

The use of combined vitamin and mineral therapy in addition to the standard one with the application of ESPEN recommendations as well as the monitoring of the patient by a team of doctors led to a significant reduction in the symptoms of the metabolic syndrome. A clinical research is planned in which they would apply this therapy to a larger number of subjects and thus draw more precise conclusions.

Topic: 1.12 Pediatric and adolescent endocrinology

P080 Ovarian new growth in mixed gonadal dysgenesis: a case report

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Disorders of sexual differentiation may occur as a result of discordances during either chromosomal, gonadal, or phenotypic differentiation. Gonadal dysgenesis is a rare disorder of sexual differentiation, which is characterized by the loss of germ cells in developing gonads. Different types of gonadal dysgenesis includes pure and partial gonadal dysgenesis. Partial gonadal dysgenesis includes mixed gonadal dysgenesis. This disorder is seen in patients with a 45,X/46,XY mosaicism karyotype, with an estimated 15% tumor risk.

The index patient was a 13 year old patient with ambiguous genitalia presenting with an enlarging abdominal mass. She was born full term, in a local hospital, to a 19 year old primigravid via spontaneous vaginal delivery, with no complications. Upon delivery, there was note of an ambiguous genitalia, but the medical team on duty considered patient to be phenotypically female and thus was raised as a female. Developmental milestones were at par with age. Sexual development was monitored. Pubic hair was noted at age 10, followed by growth of axillary hair at age 11. There was no breast development and no menarche.

Complete work-up included imaging and karyotyping. Karyoptyping revealed a mosaic monosomy X with cell line with marker chromosome. Further testing with FISH revealed a mosaic monosomy X with a male cell line with a derivative Y chromosome. An abdominal CT scan with triple contrast revealed the following result: a heterogenously enhancing pelvo-abdominal mass, indicative of neoplasm of undetermined origin; left posterior pelvic region soft tissue mass (which may be part of a larger mass or a separate etiology); tubular structure in the anterior pelvic region which appears to be a penile shaft with adjacent prominent soft tissue in both sides; no discrete testicle in the hypoplastic/small scrotal sac; right pelvocaliectasia. Transrectal and transabdominal ultrasound revealed: an abdominopelvic mass, consider ovarian new growth, left, probably malignant by Sassone=14, Lerner=7; malignant by IOTA LR2=67% risk of malignancy; uterine hypoplasia with thin endometrium, small-sized ovary.

She was diagnosed with mixed gonadal dysgenesis, with a consideration of a malignant ovarian new growth. The patient underwent surgical management and was advised subsequent chemotherapy. Management was multidisciplinary and was individualized to the patient.

Topic: 1.12 Pediatric and adolescent endocrinology

P081 Diagnosis and treatment of precocious puberty in the Mexican population: a case report

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Context
The central precocious puberty (CPP) is due to a activation of hypothalamus-pituitary-gonad (HPG), more frequent In female sex with a 10:1 ratio, however in Mexico there are no population data on incidence.

Objetive
To present the case of a 3-years-old female with diagnosis of CPP and review of the literature.

Method
Descriptive-transversal-retrospective study.

Pacient and interventions
4 years old female, with favorable perinatal development. Brought to assessment by mother who refers the presence of breast button and fine suprapubic hair predominantly in mons pubis, without menarche. At physical examination supralabial hirsutism, with a height of 1.06 meters. Laboratory report of progesterone 0.3 ng/ml, TSH 1.6, free t3 3.3, total testosterone 0.02, ACTH 59.2, GH 6.54, FSH 0.02, LH 0.02, SHGB 118.9, dyhidrotestosterona 0.20, total estrogens 106.10, without modifications. Suprapubic ultrasound reports a uterus withouth modifications with a cervical length of 20 mm, with the presence of a probable paraovarian cyst with a volume of 6.8 ml. The pediatric endocrinology integrate the diagnosis of probable congenital adrenal hyperplasia and decided to initiate treatment base on prednisolone, revaluation without improvement showing increase in breast size and amount of suprapubic hair, with laboratories within normal parameters, reason why the origin of hyperandrogenism and development of secondary sexual characteristics due to some adrenal alteration is ruled out, integrating by clinical diagnostic exclusion of CPP, initiating treatment based on GnRh analogs, based on triptorelina every 84 days.

Results
decrease of suprapubic hair y breast growing stop without secondary effects to the treatment, with no evidence of growth cartilage oscillation. Still follow.

Conclusion
The CPP is defined as premature onset of function of HPG, considered in our population before 8 years old. In natural history, the CPP conditions a shorter size than the expected, a decreased in bone mineral density, conditioning a higher risk of osteoporosis, a precocious development of secondary sexual characters, an menarche at less age than habitual, with the consequent early ovary fail, predisposing CV an cancer, coupled with psychosocial problems. The essential points for the diagnostic are the clinical data that they present, mainly oriented on the tanner scale. In Mexican population, we don't count with a specific scale to classify the sexual character development.

Topic: 1.12 Pediatric and adolescent endocrinology

P082 Abnormal menstrual function in adolescents with adnexal torsion

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Context

Menstrual dysfunction is characterised by high prevalence among female teenagers and in the future can lead to serious deviations in the reproductive health. In particular, it may indicate adnexal torsion.

Objective

To assess the incidence and clinical manifestations of menstrual abnormalities in young patients with adnexal torsion, as well as the optimization of surgical tactics for their treatment.

Patients and methods

Twenty-five teenage girls aged 14-17 undergone a comprehensive clinical, laboratory and instrumental examination were enrolled for the study. Group 1 included 16 patients with adnexal torsion, compromised by the presence of a retention ovarian cyst, while group 2 consisted of 9 patients with the torsion of intact adnexa.

Results

The patients were hospitalised with acute abdominal symptoms. After the examination, all patients were diagnosed with adnexal torsion. Upon admission teenagers mainly complained of intense pain in the lower abdomen (100%), nausea (60%), vomiting (40%), and low-grade fever (30%). Analysis of the anamnestic data showed the impaired menstrual function in patients from group 1. Oligo-opsomenorrhea, secondary amenorrhea, dysmenorrhea, hyperpolymenorrhea were registered.

The average age of menarche for most girls was in the range of 12-14 years. The duration of periods between menstruations varied from 1,5 to 2-3 months. There were no statistically significant differences in the duration of menstruation (4,8±0,28 days). Pain syndrome with acute abdomen, as a rule, was preceded by a delay in menstruation due to the presence of a retention formation of the ovary. Menstrual dysfunction was not observed in patients from group 2 with the exception of a 15-year-old patient with a concomitant diagnosis of type I diabetes mellitus, later menarche, and oligomenorrhea. Torsion of intact adnexa could be due to the anatomical features of the internal genital organs and a more mobile way of life. Patients of both groups underwent 25 surgical interventions in the form of laparoscopy with organ-preserving surgeries. In the absence of necrosis, detorsion was performed.

Conclusions

Adnexal torsion is an urgent condition which requires emergency gynecological care. Menstrual irregularities as “precursors” of this condition can be observed in patients with compromised ovaries making it possible to timely diagnose the presence of retention formations and prevent complications, accompanied by acute abdomen.

Topic: 1.12 Pediatric and adolescent endocrinology

P083 Clinical and laboratory profile analysis of genital ambiguity in girls with congenital adrenal hyperplasia diagnosed in public neonatal screening program in southern Brazil

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Background

Congenital Adrenal Hyperplasia (CAH) results from enzymatic defects in the synthesis pathway of cortisol, aldosterone and androgenic hormones, diverting the metabolic pathway for steroid synthesis. In girls, exposure to androgen excess can lead to virilization of the external genitalia, which can be quantified by the Prader scale.

Objective

To correlate hormonal changes with the degree of genital ambiguity assessed by the Prader scale in female patients diagnosed with CAH through a Public Neonatal Screening program in Southern Brazil.

Method

Cross-sectional study of female patients diagnosed with classical CAH from may 2014 to April 2019. Correlation between 17-OH-progesterone, androstenedione and total testosterone and severity of genital ambiguity assessed by the Prader scale. Kruskal-wallis test with Dunn's test for multiple comparisons.

Results

Seventeen female patients with classic CAH were diagnosed. Of these, three were classified as Prader I, five as Prader III and nine as Prader IV. There was a correspondence between a higher 17-OH-progesterone value and the Prader IV scale compared to Prader I ($p < 0.036$). There was no statistically significant difference between androstenedione and total testosterone values. None of the cases were diagnosed before screening and 2 were sex assigned as boys with subsequent adjustment for females.

Conclusion

CAH is a rare disease with high morbidity and mortality, presenting social and psychological issues. It is of fundamental importance to increase knowledge about virilization, in order to improve the care provided to affected patients. In our study, we found a correlation between 17-OH-progesterone levels and severity of virilization, as expected. In addition, this study highlights the importance of an efficient CAH newborn screening and a multidisciplinary approach to better approach this complex cases.

Topic: 1.12 Pediatric and adolescent endocrinology

P084 Premature ovarian insufficiency and autoimmune diseases: case report

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Context

In premature ovarian insufficiency (POI), autoimmune diseases (AID) can affect up to 30% of cases. Autoimmune Polyglandular Syndrome (APS) is characterized by the association of two or more autoimmune endocrine diseases, which may include premature ovarian insufficiency (POI). The association with non-endocrine AID is also possible.

Objective

to report a case with POI and AID

Case Description

A 15-year-old female patient started follow-up for complaints of joint pain, swelling and heat, fever and asthenia. Previous history of atopic dermatitis and asthma. Family history of thyroid disease (mother with severe Graves disease, progressing to hypothyroidism, in addition to aunts and grandmother with hypothyroidism) was present. At physical examination, height and weight bellow 3rd percentile and Tanner Stage B1PH1 stage. During investigation she developed goiter and primary hypothyroidism with positive antibodies (elevated TSH, anti TPO 70 UI/mL; anti TBG> 3000UI/mL) and autoimmune pancytopenia (hemoglobin 3.1g/dL; leukocytes 2,300g/µL; platelets 31,000g/µL) after being excluded other hematologic causes. Other complementary tests: small pericardial effusion; Fine dotted nuclear ANA (1:160); Chest CT: chronic interstitial pneumonitis; normal blood glucose; anti GAD; bilateral papillary edema; FSH of 45.8 mIU/mL; pelvic ultrasound: uterus and ovaries with prepubertal aspect. After a multidisciplinary approach, a diagnosis of POI due to autoimmune etiology was made, within the spectrum of APS. Currently, she is on immunosuppressive therapy and there is a plan for pubertal induction after stabilization of the clinical condition.

Discussion and Conclusion

In POI, autoimmune thyroid disease (ATD) may be present in up to 20%. The type III APS, in which ATD is mandatory, is classically divided into subtypes A (associated with Type I Diabetes Mellitus), B (with pernicious anemia), C (with vitiligo and haematological disorders) and D (with vasculitis and connective tissue diseases). Although rarely all spectrum of AID are present at the initial diagnosis, it was difficult to classify this patient. The possibility of a not previously described subtype of APS type III and/or another autoimmune defect cannot be ruled out. This case, in which multiple organ systems are involved, enhances the associations of AID in cases of POI, the need of an in-depth investigation of other familial cases and the importance of a multidisciplinary approach and care.

Topic: 1.12 Pediatric and adolescent endocrinology

P085 Evaluation of gynaecological problems among adolescent girls attending a tertiary care centre

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Objective

To find out prevalence of different gynaecological problems among adolescent girls.
To describe the clinical, anthropometric, lifestyle, biochemical and hormonal profile of different gynaecological problems among adolescent girls.

Method

Study Area: VPIMS, Lucknow, India.
Study population & size: 100 Adolescent girls (Age 13-19).
Data collection: Semi-structured proforma developed for the purpose of study. Demographic, anthropometric and clinical profile was noted. Menstrual irregularities were classified according to flow, volume, regularity and frequency using FIGO criteria. Results of various clinical and biochemical/USG assessments.
Data Analysis: The data was analyzed using Statistical Package for Social Sciences Version 21.0. Chi-square and ANOVA were used to compare the data. The confidence level of the study was kept at 95% hence a 'p' value less than 0.05 indicated statistically significant difference.

Results

Age at menarche ranged 11-14 years. Mean age at menarche was 12.65±0.70 years. Almost half (48%) girls had attained menarche at the age of 13 years.
Using BMI criteria, majority had BMI in normal range (70%).11% overweight and 19% underweight.
The most common complaints included pain during menstruation reported by 49% of girls, followed by heavy menstruation (24%), prolonged menstrual bleeding (10%) and whitish discharge (9%).
Pallor and tenderness were noted in 13% and 5% girls respectively. Majority of girls (57%) were anemic (Hb<12 gm/dl).
Clinico-pathological and USG assessment could establish final diagnosis in 98 girls.
Among the adolescents with menstrual problems (n=72), most common diagnosis was Dysmenorrhoea (62.5%) followed by heavy and prolonged bleeding (36.1%). Only 1(1.4%) case had disorder of endometrial origin (endometritis).
Among the adolescent girls diagnosed with hormonal problems (n=17), most common diagnoses were PCOS and thyroid disorder (29.4% each) followed by Mastalgia (23.5%) and Hyperprolactinemia (17.6%) respectively.
Out of 9 girls diagnosed with infectious problems, cause of majority (55.6%) had urinary tract infection while remaining 4 (44.4%) were diagnosed as pelvic inflammatory disease.
Significantly higher proportion of girls with hormonal problems had abnormal BMI as compared to those with menstrual and infectious problems.

Conclusions

The findings of present study showed that menstrual disorders were the most common gynaecological issues in adolescent girls.

Topic: 1.13 Thyroid diseases

P086 Defict iodine in pregnant attended the OB Hospital Maternity of Our Lady of Altagracia

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Summary

Introduction: Iodine is a trace element with multiple use, in medicine its main function is the substrate for the synthesis of thyroid hormones. Iodine may be provided by exogenous sources (food and / or drugs) and endogenous and degradation of thyroid hormones themselves. Iodine deficiency is associated with hypothyroidism, and is the only cause of preventable mental retardation but not reversible.

Goals: show that iodine deficiency in pregnant patients in the Dominican Republic is high.

Sample: Has been composed by 200 pregnants attending the OB.

Type of study: an observational cross-sectional study was conducted with prospective evidence.

Results

Of the 200 patients, 83 to 41.5% iodine deficiency present, despite the daily food consumption which are important sources of iodine (salt, marinades, fish etc.). Iodine deficiency was present during all trimesters with 36% in the first quarter.

Recommendation: conduct multicenter study covering a larger population and monitoring mother newborn children with iodine deficiency, it promotes good eating habits and supplementation with multivitamins containing iodine during pregnancy and lactation preconception stage.

In developing countries, iodine deficiency has been identified as one of the modifiable factors that have an adverse effect on child development. It is a global public health problem.

Iodine requirements vary depending on age and physiological conditions, the daily requirement of iodine according to the WHO are: 90mcg 0-5 years, 6-12 120mcg, over 12 150mcg, pregnancy 250mcg. Doses greater than 500, does not provide additional benefits, and may be associated with thyroid dysfunction. Especially through the use of unregulated supplements algae. Iodine has renal excretion so quantification of iodine in urine is the most specific method.

The Public Health Committee of the American Thyroid Association reported that women take a daily multivitamin with 150 mcg of iodine.

Conclusions

41.5% of the 200 patients investigated iodine deficiency present in urine.

The pre-pregnancy or during pregnancy developed hypertensive disorders was the most frequent antecedent staff 17%. The study involved 15 patients with disorders carbon hydrates (diabetes mellitus type 1, 2 and gestational) of which 11 corresponding to 73.3% resulted with iodine deficiency, increasing maternal fetal morbidity and mortality.

The diet includes food consumption containing iodine as iodized salt, deep water fish, in contrast to only 10 users refer using non-iodized salt.

Topic: 1.13 Thyroid diseases

P087 Retrospective study on pregnancy and hypothyroidism effects in Libya

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Context
Pregnancy is one the most important events in women life. Pregnancy can alter the thyroid hormone and by its effect on the glands. One of the most important dysfunctions is hypothyroidism. Which can have adverse effects on the neonates. Iodine deficiency is the most common cause of hypothyroidism in the world.

Objective
In this study, we aim to describe the pregnancy outcomes in patients with hypothyroidism.

Methods and Patients
This is a retrospective study conducted in Libyan hospitals. Subjects were categorized into three groups: Normal, hypothyroidism, and hyperthyroidism. Clinical, endocrinological and treatment modalities were assessed. Twenty patients with hypothyroidism were assessed. They were investigated for thyroid stimulation hormone (TSH), free tri iodothyronine and free thyroxine levels. The most common symptoms were fatigue and headache. All pregnant ladies were given thyroid hormone replacement after the diagnosis.

Results
Among the twenty patients who were assessed. Three (15%) of them have a history of recurrent abortion. Four (20%) of them have a history of hemorrhage during pregnancy. Five (25%) of them have intrauterine growth restriction (IUGR) in their fetuses during ultrasound surveillance. During follow up, about seven (35%) of them had preterm delivery. Some of the neonates displayed lower APGAR Score of less than 6.

Conclusions
The results of the current study demonstrated that pregnant ladies have higher compilations and adverse outcomes compared to the normal population, which necessitate the screening of thyroid functions during pregnancy in the Libyan hospitals.

Topic: 1.13 Thyroid diseases

P089 Do hypothyroid in anti natal care affect maternal fetal outcome - a diagnostics, predictive and prescriptive approach

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Context
The motivation was hypothyroid (HT) confirmed at 15% in South Indian setting (SI) at KG tertiary. The Maternal risk and fetal complications (MRFC) occurred. There was not much papers on prognosis of MRFC; also no specific cutoff on TSH, FT4, FT3 (Thyroid Markers TM). Normal delivery (ND) was in question

Objective
Patient: prevent MRFC
Providers: cut off point for HT, subclinical, overt
Predictor for birth weight MRFC and dosage.

Methods
The overall distribution (n=160) for TSH and a measurement (KGSwapnaChandRa) Kg constant was statistically found from TM to predict MRFC, dosage

Intervention
Levo Thyroxine and LSCS

Main outcome measure
KG constant and Predicting ND and MRFC

Result
1/ sqr (TSH*T4/T3) called Kg constant was found if Below 0.331 was overt for higher dosage upto 100 mcg, from 0.332 to 1.256 for low dosage and above 1.257 subclinical for medium dosage. An increase of T4 by 0.1 units increases Birth weight by 100 grams. Chance for zero defect on MR at 93%for HT and 95%for ET and on FC at 92% for HT 94% for ET was reduced for overt (56%) and other subclinical at 69%.
The Kg constant was significant respectively for overt, subclinical and HT were 0.2498, 1.35 and 0.8025.

Conclusion
T4 must be checked for all cases and Kg constant be used for deciding overt and dosage. ND and birth weight were not normal when Kg constant below 0.331 of overt cases. The 15 symptoms were required to be noted for management of every HT cases.

Topic: 1.13 Thyroid diseases

P090 Hypothyroidism and comorbidity at elderly

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Introduction

Hypothyroidism is very important entity especially at elderly patients. It can be seen as an increase of TSH, but also as an decrease of the concentration of thyroid hormones. A distinct entity is subclinical hypothyroidism where only an increase of TSH can be seen. Ageing causes an increase in incidence of diseases associated with thyroid gland since physiologically at elderly there is a higher level of TSH in the serum. Even, some American associations suggest that a screening for hypothyroidism should be performed at population older than 60 years.

Depletion of thyroid hormones cause a transformation in epithelia of blood vessels and that could be a huge problem in elderly patients. Atherosclerosis, dislipidemia and hypertension can usually be seen together and that is proven in many studies. There is also a positive correlation between depletion of CHF and hypothyroidism. Also, some studies are showing an increase in morbidity in elderly patients with hypothyroidism. All of this indicates on importance of early diagnosis and therapy at elderly.

Objectives

Diabetes mellitus, hypertension, CHF, coronary disease, dementia, TSH level, cholesterol with fractions and triglycerides are parameters that have been followed. We analyzed in which percentage these comorbidity are present.

Methods

In this study we included 100 random patients that had been treated at the Clinical Institute of Geriatrics "KBC Zvezdara", Belgrade from January 2019 till December 2019. Average age is 71,3 years. We included 10 male patients/10%/ and 90 female patients/90%/. All patients have a diagnosis of hypothyroidism and are on the substitution therapy. Length of illness is between 3 and 15 years.

Results

Female patients are more numerous, presence of T2DM is 48%, hypertension 62%, none of the patients had dementia, coronary disease is present in 10,3% and CHF in 17,4% of cases. Average values of total cholesterol are 5,93, HDL 1,98, LDL 2,43, triglycerides 1,64. Average value of TSH is 3,81.

Conclusion

In hypothyroidism comorbidity are present in a high percentage at elderly even though regulation of thyroid hormones is good. Females are especially at risk. Early diagnosis is of a great importance.

Key words: hypothyroidism, elderly, comorbidity.

Topic: 1.13 Thyroid diseases

P091 Correlation between thyroid stimulating hormone level and androgens in euthyroid hyperandrogenic polycystic ovary syndrome

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Context

Thyroid dysfunction is frequently present in women with polycystic ovary syndrome (PCOS). Some recent data confirmand association between thyroid autoimmunity and PCOS. While the causality of this association is still uncertain, the two conditions share a bidirectional relationship, but there are many other possible factors such as increased insulin resistance, which is present in both disease states, seem to play a complex role in connecting these two disorders.

Objective

The aim of our study was to compare thyroid stimulating hormone (TSH) levels between euthyroid PCOS and euthyroid control women and to investigate possible interrelationship between TSH level and androgens as well as TSH and insulin resistance in these women.

Patients and Methods

Cross-sectional study including 133 PCOS and 45 age, body mass index (BMI), euthyroid and with negative thyroid autoimmunity-matched women (PCOS- BMI 27.33 ± 0.72, age 28.16 ± 0.52), control women- BMI 27.76 ± 1.30, age 30.39 ± 1.03).

Results

The TSH level was higher (2.32 ± 0.09 vs. 1.92 ± 0.15, $p < 0.05$) in hyperandrogenic PCOS than in control women. Testosterone levels was significantly higher (2.44 ±0.09 vs. 1.61 ± 0.13, $p < 0.001$), FAI was higher (9.80 ± 0.91 vs. 5.57 ± 1.67, $p < 0.05$), androstendione was higher (3.22 ±0.15 vs. 2.50 ± 0.29, $p < 0.05$) and DHEAS was also higher (7.12 ± 0.31 vs. 4.88 ± 0.49, $p < 0.001$) in PCOS than in controls. SHBG was significantly lower (38.47 ±2.17 vs. 63.75 ± 6.72, $p < 0.001$) in PCOS than in control women. HOMA IR was similar in both group (3.7 ± 0.28 vs. 3.01 ± 0.35, $p > 0.05$). There were no correlation between TSH and testosterone, DHEAS, but TSH level is positively associated with androstendione ($r= 0.245$, $p < 0.05$) and negatively associated with SHBG (-0.203, $p < 0.05$).

Conclusions

Higher TSH level is confirmed in euthyroid PCOS women in comparission with controls women. Positive correlation between TSH and androstendion suggested possible interrelationship between thyroid function and PCOS, as well as possible relationship thyroid function and insulin resistance having in mind significant negative association between TSH and SHB levels in PCOS.

Keywords: polycystic ovary syndrome, TSH, testosterone, androstendione, DHEAS, SHBG, HOMA IR

Topic: 1.14 Endocrine disorders and woman's health

P092 Vaginal microbiome of women with premature ovarian insufficiency: descriptive cross-sectional study

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Context
The knowledge of the vaginal flora of women with premature ovarian insufficiency (POI) are scant, in special in women using systemic hormone therapy (HT). Probably this is the first study using microbiome, a modern technique.

Objective
To describe the vaginal microbiome of women with POI using HT.

Methods
Descriptive cross-sectional study.

Patient(s)
Forty women with POI receiving systemic HT for at least 6 months were included in the study carried out at the Department of Obstetrics and Gynecology of the School of Medical Sciences, University of Campinas - UNICAMP. Intervention: Vaginal secretion was collected for DNA extraction followed by Pyrosequencing of the 16S rRNA. The samples were pooled into phylogenetic groups (Ravel – I, II, III, IV, V).

Main outcome measure
Vaginal microbiome according to Ravel groups.

Results
Women had a mean age of 37.13 (± 7.27) years and POI diagnosis at 27.90 (± 8.68) years, a mean HT duration of 8.20 (± 8.73) years. It was observed that 33.4% of the women presented group I flora, with a predominance of L. crispatus; 9% group II flora, with a predominance of L. gasseri; 33.4% group III flora, with a predominance of L. iners; 15.2% group IV flora, with a predominance of anaerobic bacteria; and 9% group V flora, with a predominance of L. jensenii.

Conclusion
Women with POI receiving HT presented a vaginal microbiome with a predominance of lactobacilli in the composition of the vaginal flora, specifically L. crispatus and L. iners when evaluated by molecular biology through the pyrosequencing of 16S rRNA.

Topic: 1.14 Endocrine disorders and woman's health

P093 Evaluation of serum kisspeptin levels in patients with premature ovarian insufficiency

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Context
Premature ovarian insufficiency (POI), commonly used in literature as the occurence of hypergonadotropic hypogonadism before the age of 40. Although POI affects about 1% of women in reproductive age, the etiology is still unknown for most cases. kisspeptins are a family of peptides that are involved in many endocrine systems, especially reproductive endocrine systems, which trigger puberty and are thought to play a role in regulating ovulation.

Objective
In this study, we aimed to compare serum kisspeptin levels between POI and healthy women.

Methods
In Cerrahpasa Medical Faculty, Department of Obstetrics and Gynecology, Istanbul University-Cerrahpasa, 45 women diagnosed with POI and 45 healthy regular menstruating women to form the control group were included in the study. Serum samples were stored at -80 ° C.
Demographic findings and FSH, LH, AMH, Estradiol, TSH, Prolactin levels and body mass indexes (BMI) were determined in all women. Serum kisspeptin levels were measured. Statistical analysis of results was done in SPSS program Version 21.

Results
There was no significant difference in terms of height, weight and BMI between POI patients and control women. The ratio of systemic diseases and early menopause in the family were higher in POI group than control group. Women with POI had lower FSH and LH levels and higher Estradiol and AMH levels than control group. There was no significant difference in term of TSH levels between two groups. The median kisspeptin level of POI was lower than control group [0.86 (0.13-2.97) vs 1.56 (0.41-2.99) ng/L, p=0.038, respectively]. Serum kisspeptin concentrations were significantly negatively correlated with age (r=-0.267, p=0.011) and significantly positively correlated with AMH levels (r=0.221, p=0.036). The other parameters did not correlate with serum kisspeptin level.

Conclusion
In this study, we found that kisspeptin levels are lower in POI patients compared to control group. The level of kisspeptin is correlated with AMH and age, therefore we suggest that diminished level of kisspeptin are due to decreased secretion of ovarian kisspeptin with reduction of ovary functions. Further investigations are required for this statement.

Topic: 1.14 Endocrine disorders and woman's health

P094 Pregnancy follow-up in primary hyperparathyroidism – case presentation

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Introduction

The evolution of spontaneous pregnancy in patients with known primary hyperparathyroidism and hypercalcemia, is a rare and difficult task concerning the safety of the fetal development.

Objectives

Our case presents the evolution in preconception, pregnancy and postpartum period of a 28 year female, previously known with primary hyperparathyroidism.

Material and Method

A 28 year old female was diagnosed in February 2016 with symptomatic primary hyperparathyroidism.
Clinically she presented increased heart rate episodes, most frequently during night sleep period.
Complete ultrasound evaluation was performed with a Hitachi Preirus ultrasound machine, with a linear multifrequency probe, using conventional, Color Doppler and strain elastography technique: visualization of left inferior parathyroid.
Scintigraphy evaluation showed an image of minimum overactive left inferior parathyroid gland.
Complete biochemical profile was performed.
The recommendation at diagnostic was surgical removal of the parathyroid gland.
Despite treatment recommendation, the patient did not undergo surgery, the biochemical markers increased (August 2016) with proportional increase of the parathyroid volume (ultrasound evaluation). Unplanned pregnancy appeared in December 2016.
Monthly biochemical follow up of the maternal calcemia were performed.
The pregnancy outcome was natural delivery, week 38, male, neonatal Apgar score 10. Active screening for functional hypoparathyroidism in the neonate ward was performed. The mother underwent parathyroidectomy in the postpartum period. Fluctuant hypoparathyroidism – initial functional, late onset definitive - did develop.

Conclusion

Unplanned pregnancy follow-up in a treated symptomatic primary hyperparathyroidism case is a rare and difficult case. Treatment options are limited during the pregnancy course; watchful waiting of the maternal levels of calcemia and dietary counseling are the only tools available. Emergency parathyroidectomy, if the calcium levels exceed the safety threshold, is the only available interventional tools.

Topic: 1.14 Endocrine disorders and woman's health

P096 Reproductive health of female adult survivors of papillary thyroid carcinoma

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Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine cancer affecting mainly women aged 30-39 worldwide. PTC patients have favorable prognosis. However, they are found to have imbalances in estrogen metabolism, changes in potentially cancerogenic estrogen-DNA adducts, and considerable fluctuations in thyroid homeostasis caused by medical PTC treatment, which can be risk factors for both hyperproliferative pathologies of the reproductive system and estrogen-dependent cancers.

Objective

To determine the frequency and structure of reproductive system disorders in young adult female survivors of papillary thyroid carcinoma.

Methods

We analyzed medical records and performed a follow-up examination of 110 women aged 20 to 45 years who had undergone thyroidectomy for PTC. The control group included 90 age comparable females with normal thyroid status. Based on the time of thyroid cancer diagnosis, women from the main cohort were divided into three groups: group I (n = 31) - 1-5 years after cancer diagnosis, group II (n = 42) - 5-10 and group III (n = 37) - ≥10 years after cancer diagnosis.

Results

The average age of the subjects was 36.7 ± 6,32 years. Adenomyosis was diagnosed 3 times more often (95% CI 1.47-6.33) in women from the main cohort compared to the controls (60.9% versus 20% ($p < 0.05$)). Combination of adenomyosis and uterine leiomyoma was revealed in 17.3% of women in the main cohort, which was 2.6 –fold more frequent (95% CI 1.08-6.21) than in those from the control group where the concomitant pathologies were diagnosed in 6.7% of cases. Among other reproductive health disorders diagnosed in the main cohort were menstrual disorders, uterine leiomyomas, endometrial polyps, however, no statistically significant difference was found when compared with controls. Analysis of reproductive health disorders by group based on the time of thyroid cancer diagnosis revealed no statistically significant difference, except for the fact that endometrial polyps predominated in groups I and III (I-19.4%; II-2.4%; III -18.9% $p<0.05$).

Conclusions

Adenomyosis ranks first in the structure of reproductive health disorders in the history of female adult survivors of thyroid cancer. The lack of correlation between the incidence of adenomyosis and the time of the thyroid cancer diagnosis may suggest the possibility of common mechanisms for the development of these pathologies.

Topic: 1.14 Endocrine disorders and woman's health

P097 Regularity of menstrual cycles in extremely obese women

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Context
Irregular menstrual cycles are a sign of impaired reproductive health resulted from many diseases and endocrine disorders, including the overweight and obesity. Obese women are more likely to have hormonal changes, insulin resistance, elevated serum testosterone levels, lower sex hormone-binding globulin, affecting menstrual dynamics and leading to irregular menstruation, oligomenorrhoea and amenorrhea.

Objective
The objective of the study was to examine the association between obesity and the regularity of menstrual cycles in women of the reproductive age.

Methods and Patients
The study included 118 extremely obese women of the reproductive age. Anthropometric parameters, body mass (TT), body height (TV), body mass index (BMI), waist circumference (OS), and hip circumference (OK) were measured. All women were monitored for the onset of menarche, the regularity of menstrual cycles, the duration of irregular menstrual cycles, and the duration of obesity. Patients were divided according to age: I < 35 years and II >35 years. The statistics were performed in IBM SPSS version 20.

Results
Anthropometric characteristics of the subjects were: Body weight 119.58 ± 22.51kg, BMI 43.72 ± 8.18kg/m^2, Waist circumference 122.8 ± 16.37cm, Hip circumference 135.18 ± 16.54cm. I group: average age of 27.50 ± 5.58 years, menarche 10.45 ± 4.26 years; obesity duration was 5.88 ± 4.55 years, irregular menstruation period 5.69 ± 4.74 years. In this group, 24.2% of women had irregular menstrual cycles. II group: average age of 41.14 ± 4.18 years, menarche 9.53 ± 4.14 years; the duration of obesity was 9.91 ± 7.76 years; with irregular menstrual periods 7.38 ± 7.18 years. In this group, 29.1% of women had irregular menstrual cycles. In the group of young obese women, menstrual irregularity was associated with duration of obesity (p <05). In the group of obese patients older than 35 years, the irregularity of menstruation cycle was increased with the years of the reproductive life.

Conclusions
With aging, obese women of reproductive age are more likely to have irregular periods. These have important clinical implications of prevention and treating obesity during reproductive life. The early treatment of young women's obesity and weight reduction are crucial for maintaining reproductive health.

Topic: 1.14 Endocrine disorders and woman's health

P100 Reproductive health features of young women with type 1 diabetes mellitus born by mothers with type 1 diabetes mellitus

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Background

Leading position among endocrine pathology of adolescence and young women is type 1 diabetes mellitus (T1DM), which in recent years has a strong increasing incidence as well as strong hereditary factor. Among young women with T1DM reproductive dysfunction is one of the current problems of modern endocrine gynecology.

The purpose was to investigate the features of reproductive health in 38 young women (18-22 years old) with T1DM born by mothers with T1DM.

Methods

Retrospectively we studied the features of puberty and prospectively examined levels of blood glucose and Hb A1c, levels of gonadotropin (LH, FSH) and sex hormones (prolactine, estradiol, progesterone, testosterone) in peripheral blood (ELISA, France), determinated antibodies to ovarian tissue (Euroimmune, Germany) and provided pelvic ultrasonography (MyLabSeven, Italy).

Results

The proportion of patients with delayed puberty and physical development with the debut of T1DM in the pre-puberty is 71,1 %, in the early puberty (3-7 years) – 18,4 %, in the active adolescence (11-14 years) – 5,3 %, in the post-puberty (over 14 years) – 5,2 %. Ovarian failure occurred in 81,76% of the patients with T1DM and was expressed in increased levels of LH, estradiol and free testosterone.

The positive correlation was detected between the blood levels of estradiol (r= 0,68), testosterone (r= 0,54), progesterone (r= 0,50) to the level of Hb A1c.

We revealed correlations between the levels of sex hormones and the regime of insulin therapy. Autoimmune ovarian failure was also detected in 5,3 % cases. The presence of ovarian insufficiency was accompanied by increased number of antral follicles in them.

Conclusion

T1DM adversely affects future reproductive health formation of young women born by mothers with T1DM, which is predominantly realized by hormonal dysfunction, ovarian failure and pathological changes in the structure of the ovaries.

Topic: 1.14 Endocrine disorders and woman's health

P101 Reproductive state in women with kidney transplant

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Chronic kidney disease (CKD) is a global burden, with prevalence of 11-13%. CKD usually remains asymptomatic until later stages, but is strongly associated with increased risks of cardiovascular morbidity, premature mortality and decreased quality of life. Kidney transplantation (KT) is a treatment of choice for end stage CKD. KT was performed 350 times from dead donor and 6 times from living donor in the GU "Minsk Scientific-Practical Center of Surgery, Transplantation and Hematology" in 2018.

Objective

Evaluate reproductive state in women with KT. Patients' history was collected by interview and physical examination, hormone levels were determined by ELISA. Ethics Committee approved the study. All patients signed written informed consent. Research group includes 34 women of age 36,4 ± 5,8 who had undergone KT within last 6 years. Patients have adequate graft function confirmed by serum creatinine, urea, cystatine C levels and GFR. Patients get immunosuppressive medications (Medrol-Ciclosporin/ Azathioprin/Tacrolimus- Mucophenolate mofetil) in 2 or 3 component treatment regime and had no complications or concomitant diseases at the time of the study. Women who had severe infections, were pregnant or had complications in graft functioning were excluded from the study. Control group consisted of 27 healthy women. Measures showed 27 patients had menstrual disturbances, the most common oligo- and amenorrhea that depended from age and time that a patient had spent on the dialyses. Average levels of LH, FSH and estradiol were similar both in the follicular and luteal phases of menstrual cycle. Levels of progesterone were comparable, both groups showed presence of ovulation, but the levels of Antimullerian hormone was statistically lower in women with KT (p=0,0443). Serum prolactin levels were higher in kidney recipients that in controls (p=0.01) with the ranges 693,5± 267,7 mIU/L (KT) and 510,0±271,8 mIN/L (healthy women). Testosterone and free testosterone levels we significantly lower in women after KT than in control ones. 25(OH)D status remained below recommended threshold in both groups that was explained by the autumn/winter time of the study. Women after transplantation suffer from irregular menses, decreased ovarian reserve, hyperprolactinemia, low levels of testosterone. Different hypotheses suggest connection between immunosuppressive therapy, dialyses time, graft function and obtained data that needs further investigation.

Topic: 1.14 Endocrine disorders and woman's health

P102 46, XX DSD with ambiguous genitalia, gynecomastia and male gender identity: a case report

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Context

Ovarian differentiation is the normal pathway in 46,XX foetus, but in rare cases, 46,XX gonads may differentiate into testes or give rise to the coexistence of ovarian and testicular tissue, conditions known respectively as 46,XX testicular and ovotesticular DSD. Differentiation in testicular tissue may be due to the translocation of SRY gene to the X chromosome or an autosome. In SRY-negative XX gonads, two different mechanisms may underlie the development of testicular tissue: overexpression of other pro-testis genes (e.g. SOX family genes) or failure of pro-ovarian/anti-testis genes, (e.g. WNT4 and RSPO1). Recent experimental and clinical evidence giving insight into SRY-negative 46,XX testicular or ovotesticular DSD is discussed.

Case report

We describe a case of a Cameroonian 17-year-old patient assigned as male at birth and with a male gender identity. He asks for adjusting his phenotype to his male gender identity with surgery and hormonal treatment. His height and weight were 160 cm and 70 kg, respectively, with a BMI (body mass index) of 27.3 kg/m^2. He presented sparse body hair and bilateral gynecomastia. The genital examination showed hypospadias, small penis size, small testes (both 3 mL), and sparse pubic hair (Tanner stage II). No vaginal orifice was detected. Standard abdominal and pelvic ultrasounds showed no significant abnormalities, small prostate gland (16x10 mm) around the upper vagina (40x16 mm) and urethra while no residual Müllerian structures were identified. Pelvic MRI confirmed data obtained with ultrasound, except for a fluid formation (22x10 mm) close to iliac vessels (hypoplasic ovary?).
Hormone analysis revealed hypergonadotropic hypogonadism: FSH and LH mIU/mL 21 and 22,5 mIU/mL respectively, total testosterone (TT) 3,4 ng/mL, estradiol (E2) 37 pg/mL and anti-mullerian hormone (AMH) 0,36 ng/ml.
Karyotyping was performed on peripheral blood lymphocytes and showed a 46,XX karyotype. Fluorescent in situ hybridization (FISH) was carried out using the LSI SRY/CEP X probe showed no evidence of sex-determining region Y (SRY-negative). CGH-Array analysis does not identify any unbalanced chromosomal abnormalities.

Conclusions

We report a case of 46, XX male DSD SRY- negative and with no evidence of unbalanced chromosomal abnormalities involved in sex determination cascade. Our aim is to gain insight about genetic features of this 46, XX DSD before proceeding with the requested treatment.

Topic: 1.14 Endocrine disorders and woman's health

P103 Comparison of Urinary 6-sulfatoxymelatonin Levels of Patients with Diabetes Mellitus Type 1 and Endometriosis

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Context and Objective

Melatonin is an integral part of the homeostatic mechanism in the body. The decreased melatonin excretion has been reported to be associated with various diseases including genital endometriosis (E) and diabetes mellitus type 1 (DM1). The urinary metabolite of melatonin, 6-sulfatoxymelatonin (MT6), has proved to be a reliable index of melatonin production.
The proposed study aims to evaluate the level of urinary aMT6s in women of reproductive age with DM1 and E.

Materials and methods

Our study was performed in four groups of patients. Urine samples were collected from 62 patients merely with DM1, 68 patients solely with E, 17 patients with diabetes and endometriosis (DM1+E), and 15 women without DM1 and E who served as a control group. Diagnosis of E was confirmed by laparoscopy and histological examination, which was conducted afterwards. All patients with DM1 did not have any evidence of proliferative diabetic retinopathy. The level of MT6 in specimens was measured using enzyme-linked immunosorbent assay (ELISA) and compared between the four groups. Comparisons between the groups were made by unpaired t-tests.

Results

The urinary MT6s (mean ± SD) levels were 1517.1 ± 189.4 ng/h, 1257.9 ± 111.7 ng/h, 1199.9 ± 198.4 ng/h and 941.6 ± 177.9 ng/h in the control groups and in patients with DM1, E, and DM1+E, respectively. The urinary MT6s level of the DM1+E group was significantly lower than that of the control ones ($p<0.05$). Despite the fact the MT6s levels in patients with E and in patients with DM1 groups were lower than in the control group; however, it did not demonstrate any significant difference ($p>0.05$).

Conclusions

There was a decrease noted in the urinary levels of MT6 in both groups of patients with DM1 and with E compared with the control group; however, the statistical evidence demonstrated the unreliable results, which may be further reflected on the level of variability. The significant decrease in the level of MT6 was observed with DM1+E group, which indicates the fact that the decreased urinary MT6s level may be associated with the pathogenesis of E in DM1 patients. The further detailed research is necessary in order to determine the role of melatonin in pathogenesis of these diseases and the possibility of melatonin usage in the therapy.

Topic: 1.14 Endocrine disorders and woman's health

P104 Hypoxia Preconditioned Human Umbilical Cord Mesenchymal Stem Cells Improve Ovarian Function in Premature Ovarian Insufficiency Mouse Model

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Context

Premature Ovarian Insufficiency (POI), 1-3% of adult women being affected, has a profound impact on physical and mental health. Recently, much more attention has been paid into the research of human umbilical cord mesenchymal stem cells (hUCMSCs) for repairing effected after ovary injury.

Objective

To investigate the therapeutic effect of hUCMSCs and also with the precondition of hypoxia on POI mice model.

Methods

Hypoxia preconditioning was achieved by culturing hUCMSCs under a hypoxia environment. Busulfan and cyclophosphamide-induced POI mouse model were established, were randomly divided into four groups: a nomal control group (n = 15, A), a POI group (n=15, B), POF plus cell transplantation group (hUCMSCs were implanted into the tail vein, n =15, C) and POF plus cell transplantation by oxidative stress group (n =15, D). Four weeks after transplantation, mice were sacrificed for sampling. Ovarian reserve was evaluated using follicle counts and AMH expression. For ovarian function sex hormone levels were assessed (E2, FSH).

Results

Compared with group A, group B presented a decrease in primordial follicles and growing follicles and a significant increase in atretic follicles ($p < 0.05$). The number of growing follicles in group C and D increased significantly ($p < 0.05$) and the atretic follicle numbers significantly declined compared with group B ($p < 0.05$). Compared with Group A, group B clearly displayed worse ovarian function. In group C and D, serum levels of E2 significantly increased compared to group B ($p < 0.05$).

Conclusion

hUCMSCs transplantation can significantly improve the serum levels of high gonadotropin and low estrogen of POI mice and can promote follicular development. Transplantation of hypoxia-preconditioned hUCMSCs exerted better therapeutic trending.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support (XMLX201710); Beijing Municipal Administration of Hospitals' Ascent Plan(DFL20181401); Beijing Obstetrics and Gynecology Hospital, Capital Medical University (FCYY201811); Beijing Hospitals Authority Youth Programme (QML20181401); Capital Medical University Research and Development Fund (PYZ2018161).

Topic: 1.15 Endocrine disruptors

P105 The significance of bisphenol a release from dental restorative materials for the human exposure

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Context
Bisphenol A (BPA) is one of the widest-spread and most-discussed endocrine disruptors because of its estrogenic activity which affects human reproduction. Furthermore, higher BPA levels were detected in women with the polycystic ovary syndrome, and transplacental transfer of BPA may affect the fetal hormonal homeostasis. BPA is contained in plastics, epoxy resins, dental materials, or thermal paper but some "BPA-free" alternatives were recently marketed. However, the content of BPA does not simply imply a health risk because its release is dependent on how BPA is bonded within the material and on several external factors. Therefore, in order to evaluate the eventual risks, it is necessary to quantify the release of BPA from these materials and to describe its kinetics.

Objective
In this study, we have measured the BPA release from dental restorative materials, specifically from "conventional" composites with BPA-containing methacrylate monomers and "BPA-free" composites. For the risk assessment, the specimens were immersed in methanol because more BPA is released in organic media. The amounts of detected BPA were compared with the tolerable daily intake (TDI).

Methods
"Conventional" resin composites Charisma Classic (CC) and Filtek Ultimate (FU) and "BPA-free" composites Charisma Diamond (CD) and Admira Fusion (AF) were used. The specimens (diameter 6 mm, height 2 mm, n=5) were prepared in Teflon molds, light-cured from one side for 20 s, and incubated in 2 mL of methanol which was exchanged after 1, 4, 9, 16, and 35 days. After derivatization with dansyl chloride, BPA concentrations in the eluates were determined using liquid chromatography – tandem mass spectroscopy. The amounts of released BPA were expressed in nanograms per gram of the composite (ng/g).

Results
The total amount of BPA released from "conventional"composites (CC 67.6 3.8 ng/g; FU 56.5 5.6 ng/g) was significantly lower compared to "BPA-free" composites (CD 3.1 1.2 ng/g; AF 3.2 1.6 ng/g). The fastest release was observed after within the first day but even the highest 1-day value of FU (15.3 0.8 ng/g) was several orders below the TDI 4 g/kg bw.

Conclusions
BPA release from dental composites was detectable; however, the values were very low in comparison with the current limits. Therefore, when abiding by the instructions for use, the usage of these materials should pose no considerable health risk even for pregnant women.
Supported by Charles University, project PROGRES Q29/1LF.

Topic: 1.15 Endocrine disruptors

P106 Ovarian histological aspects of transsexual men undergoing oopherectomy after prolonged testosterone therapy

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Objective

To analyze ovarian histological aspects of transsexual men undergoing Oophorectomy after prolonged use of testosterone and its possible relation with cancer.

Methods

From a sample of twenty patients being studied in the last 2 years at the endocrine gynecology outpatient clinic of a teaching hospital, seven patients were fit for the study. The exclusion and inclusion criteria were used. In line with the literature, we gathered the ovarian anatomopathological results of the patients and compared with the outcomes already published in the literature.

Results

In the anatomopathological analysis, the prevalence of characteristics such as yellowish brown external surface, brownish cut surface of fibroelastic consistency and the diagnosis of follicular cysts with the presence of albicans bodies were observed about those patients.

Conclusion

Despite the scarcity of studies and the number of patients, some regular characteristics can be observed about the ovaries studied. Among them, there is the increase in organ volume and the appearance of follicular cysts present in most related studies. However, it was not possible to establish a clear relation between prolonged exposure to testosterone and the development of cancer, and further studies are needed to more accurately assess this relation. It is a study to be continued on such current subject.

Topic: 1.16 Selective steroid receptor modulators

P107 Molecular mechanisms of the immunomodulatory effects of raloxifene and tamoxifen

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Context

Macrophages are immune cells that play a key role in host defense against infections as well as in tissue remodeling and homeostasis. These cells are able to respond to a variety of stimuli, adopting different phenotypes depending on the activating signal and context. Recently, we demonstrated that 17β-estradiol (E2) induces an immune-tolerant and pro-resolving phenotype of macrophages that reflects the physiological role of macrophages within female reproductive tissues. However, the estrogen-induced macrophage response may be deleterious under certain circumstances, such as endometriosis and cancer.

Objective

The aim of this study was to find appropriate pharmacological modulators of the estrogen signaling in macrophages.

Method

Primary cultures of peritoneal macrophages were obtained from wild type or estrogen receptor-alpha (ERα)-knockout female mice and analyzed for the expression of anti-inflammatory genes in response to E2, raloxifene and tamoxifen, two selective estrogen receptor modulators (SERMs) widely used in endocrine-related disorders.

Results

Our results show that E2 regulates macrophage gene expression exclusively through ERα and that SERMs may act as estrogen antagonists or ERα-unrelated macrophage phenotypic modulators, depending on their dosage. The specific contribution of the G-protein estrogen receptor (GPER1) will be discussed.

Conclusion

Altogether, our results suggest that the activity of SERMs in macrophages and inflammation may drastically change in relation with increased drug concentrations, posing relevant implications for therapeutic settings associated with drug accumulation.

Topic: 2.1 New compounds for contraception

P108 Cycle control of an estetrol 15 mg and drospirenone 3 mg combined oral contraceptive in the E4 Freedom EU/RU phase 3 trial

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Context

Estetrol (E4) is a unique, naturally occurring estrogen with a long- half-life and minimal liver metabolism. E4 is currently under development for oral contraception in combination with drosperinone (DRSP). This evaluation reports cycle control and bleeding pattern data with E4 15 mg/DRSP 3 mg in a 24/4 day regimen, during up to 1 year of use.

Methods

This multicentre, open-label, phase 3 trial was conducted in 69 centres across Europe and Russia. Healthy women 18-50 years with regular cycles and a body mass index between 18 and 35 kg/m^2 were enrolled for up to 13 consecutive cycles. We evaluated cycle control and bleeding patterns based on daily electronic diaries to document vaginal bleeding and/or spotting. Bleeding was defined as blood loss that required the use of sanitary protection with a tampon, pad or, pantyliner, while spotting was defined as minimal blood loss that did not require new use of protection. One or more consecutive bleeding and/or spotting days bounded on either end by 2 bleeding and/or spotting-free days was defined as a bleeding/spotting episode. We performed descriptive intention-to-treat analyses.

Results

Of 1,577 subjects, 1,553 (98.5%) started study treatment of whom 1,353 (87.1%) were 18-35 years and 1,218 (77.2%) completed 13 cycles. The most common reasons for discontinuation were adverse events (AEs) unrelated to bleeding (n=104, 6.0%), consent withdrawal (n=86, 4.9%) and AEs related to bleeding (n=54, 3.1%). The mean number of scheduled ("withdrawal") bleeding and spotting days per cycle was 2.6 and 2.4, respectively. The proportion of subjects experiencing unscheduled bleeding and/or spotting decreased over time (Cycle 1: 23.5%; Cycle 2: 19.2%; Cycle 6: 15.6%), and remained 12.8%-15.8% for cycles 7-12. Among subjects who experienced unscheduled bleeding/spotting, the median duration of unscheduled bleeding/spotting days was 3.0 days, almost all of which was spotting (3 days in cycle 1, 2 days cycles 2 to 12). The proportion of women with cycles with no scheduled ("withdrawal") bleeding and/or spotting episodes varied between 5.6% and 8.1% (mean 7.9%) over the year. Most (92%) cycles included scheduled withdrawal bleeding with a median number of bleeding and/or spotting days of 4.0 to 5.0 days per cycle.

Conclusion

E4/DRSP in a 24/4 regimen displayed excellent cycle control and a favourable bleeding pattern.

Topic: 2.1 New compounds for contraception

P109 Estetrol 15 mg combined with drospirenone 3 mg is an effective oral contraceptive: results from the E4 Freedom EU/RU phase 3 trial

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Context

Estetrol (E4) is a unique, naturally occurring estrogen with a long-half-life and minimal liver metabolism. E4 is currently under development worldwide for oral contraception in combination with drosperinone (DRSP). This evaluation reports European contraceptive efficacy and safety data with E4 15mg/DRSP 3mg in a 24/4 day regimen, during up to 1 year of use.

Methods

This multicentre, open-label, phase 3 trial was conducted in 69 centres across Europe and Russia. Healthy women, 18-50 years with regular cycles and a body mass index (BMI) between 18 and 35kg/m^2 were enrolled for up to 13 consecutive cycles. Enrollees were categorized as starters (no oral contraceptive use within 3 months prior to first study drug intake) and switchers (oral contraceptive use within 3 months of first study drug intake). We evaluated on-treatment pregnancies in women 18-35 and 18-50 years measured by the Pearl Index (PI) and the method failure PI in at-risk cycles (cycles with no other contraceptive use), and the cumulative pregnancy rates (life-table) at cycle 13 for both age groups.

Results

In total 1,577 subjects were enrolled of whom 1,553 (98.5%) started study treatment and 1,218 (77.2%) completed 13 cycles. The primary efficacy population included 1,353 women age 18-35 years of whom 1,052 (77.5%) completed 13 cycles. Five on-treatment pregnancies occurred of which 3 were considered method failure. No pregnancies occurred in women aged 36 to 50 years. The PI for the primary efficacy population with 14,759 at-risk cycles was 0.44 (95% CI 0.14-1.03). The PI for all subjects (18-50 years) with 17,037 at-risk cycles was 0.38 (95% CI 0.12-0.89). Method failure PIs were 0.26 (95% CI 0.05-0.77) and 0.23 (95% CI 0.05-0.67) for the age groups 18-35 and 18-50 years, respectively. Four of the five pregnancies occurred in switchers; the PIs for starters and switchers were 0.25 (95% CI 0.01-1.42) and 0.61 (95% CI 0.17-1.55), respectively. No pregnancies occurred among the 89 (5.7%) women with a BMI ≥30 mg/kg2. The cumulative 13-cycle pregnancy rate for subjects aged 18-35 years was 0.45% (95% CI 0.19-1.09%) and for subjects aged 18-50 years was 0.39% (95% CI 0.16-0.94%).

Conclusion

E4 15 mg /DRSP 3 mg is a highly effective oral contraceptive with a probability of contraceptive protection for up to 1 year of usage of 99.6%. Evaluating differences in PIs for starters and switchers is limited due to the low number of on-treatment pregnancies.

Topic: 2.1 New compounds for contraception

P110 *In vitro* elution of etonogestrel and ethinylestradiol of the broken and not broken vaginal contraceptive ring Ornibel®

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Objective

The purpose of this study was to evaluate the *in vitro* elution of the active substances etonogestrel and ethinylestradiol of the vaginal ring Ornibel® after active breakage of the ring and to compare it to the standard elution and hormonal release of unbroken rings under same environmental conditions.

Material and Methods

Six vaginal rings of routine batches were broken deliberately and compared with 6 intact vaginal rings. *In vitro* elution was conducted with medium of buffer pH 4.2 with 0.05% of surfactant Kolliphor HS15. This medium is the standard one used in the analytical routine hormonal release controls of the product batches. The stability conditions established were 24 months at 5°C for broken and non-broken rings. From the corresponding readings of the peak areas of the standard solution and the test solution, the percentage of the active substance dissolved was calculated. Measurements were performed on each day between day 1 and 21 for etonogestrel and ethinyl estradiol.

Results

No elution differences were measured for both hormones between broken and non-broken vaginal rings.
The average elution for the non-broken rings was for etonogestrel on day 1: average: 119 µg/day; for the days 2-20: average: 132 µg/day and for the day 21: average: 111 µg/day. For the broken rings following values were obtained: day 1: average: 118 µg/day; days 2-20: average: 132 µg/day and for the day 21: average: 111 mg/day.
Following values were obtained for ethinylestradiol: Non-broken ring: day 1: average: 15 µg/day; for the days 2-20: average: 18 µg/day and for the day 21: average: 18 µg/day. For the broken rings following values were obtained: day 1: average: 14 µg/day; days 2-20: average: 19 µg/day and for the day 21: average: 18 mg/day.

Conclusions

Comparative in-vitro elution profiles show that both products (broken and non-broken) dissolved in a similar rate. In addition, all values were within a ± 10% required margin so that it can be concluded that the comparative *in vitro* elution's of both rings (broken and not broken) are equivalent. Therefore, broken vaginal rings display the same hormonal release for etonogestrel and ethinyl estradiol as non-broken vaginal rings and a ring breakage has no impact on this parameter.

Topic: 2.4 Emergency contraception

P113 Epidemiological aspects of women using illicit drugs in the Cracolândia region, São Paulo

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Objective

Evaluate the epidemiological aspects of the population of women using illicit drugs, who prevent unplanned pregnancy through the contraceptive implant.

Material

The GRAVIUS project with 304 women using illicit drugs who used the subdermal implant containing 68 mg of etonogestrel, voluntarily, by the Women's Health Reference Center (Pérola Byington Hospital), downtown of São Paulo city, denominated Cracolândia, between March 2014 and June 2018. The average age were 26.3 years old.

Results

The skin colors were represented by 98 (32.5%), 101 (33.4%) and 103 (34.1%) black, brown and white, respectively. The education level revealed that only 40% had at least the elementary education completed, among them only 1.3% had a university degree.
The illicit drug use started averaged 14.6 years. Most of these women are homeless (30.1%), in use of crack (36%), prefer to trade sexual services for drugs or money to buy drugs (33.4%), and have an important association with tobacco use (65.9%) and alcohol (64.6%). These are women present positive serology for syphilis (20.1%), HIV (4.8%) and hepatitis C (1%). The average age for menarche and the first sexual intercourse are 12.4 and 14.4 years old, respectively. Regarding the obstetric aspects, they had average 3.2 pregnancies and 2.7 live born children. Concerning the use of contraceptives methods, 36.4% do not use any contraceptive method, among those who use some method, 60.2% reported to use more the condom method, although, many times it is not use correctly.

Conclusion

The women using drugs in the downtown area of São Paulo are in high vulnerability situation, characterized by the low socioeconomic-cultural level, and present high risk of pregnancy, requiring a complete knowledge of the epidemiological aspects of this population, for improved perfomance regarding the specific treatment and prevention of an unplanned pregnancy.

Topic: 2.7 Contraception and adolescents

P113b Teenagers, immigrants and women with previous mental illness could be more sensitive to mood effects of hormonal contraception: an intersectional multilevel analysis

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Context
Hormonal contraception (HC) is extensively used worldwide and is fundamental to reproductive rights, but little is known about its effect on mood. Randomised trials investigating psychological side effects of HC are scant and demonstrate contradictory results, while epidemiological evidence indicates a link to depression, chiefly in adolescents. No consensus exists, but while most women using HC are unaffected many agree on the existence of vulnerable subgroups, that still need to be identified.

Objective
Analysing a large population sample, we wanted to investigate a possible heterogeneity in the effect of HC on use of antidepressants. For this purpose, we applied an intersectional approach in order to visualize how intersecting power dynamics can interact in combination with HC to predispose for mental health issues.

Methods
We created a cohort consisting of 1 054 661 women using a population wide record linkage database containing individual level information on dispensed drugs. We followed the women for one year from first prescription fill of a HC drug or from a set baseline for non-users. We created 72 intersectional strata by combing information on HC use, age, income, country of birth and previous mental illness and applied a multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA).

Patients
All women aged 12-30 years residing in Sweden on 1st January 2013 were included.

Main outcome measure
Use of any anti-depressant, meaning at least one prescription fill during follow up.

Result
HC users were overall 46% more likely to use anti-depressants than non-users. The highest absolute risks were uniformly found in strata with previous mental health issues, with highest risk in native women aged 24-30 either with low income and HC use (42%) or middle-income without HC use (43%). Immigrant girls from low income families had the lowest absolute risk (0.40%). The largest difference in anti-depressant use between HC users and non-users was found in teenagers, but also in immigrants and women with previous mental illness. 44% of the individual variance in the propensity of using anti-depressants was at the intersectional strata level and having a previous mental illness explained a large amount of the between-strata variance.

Conclusions
Our study suggest teenagers, immigrants and women with previous mental illness could be more sensitive to mood effects of HC, a heterogeneity important to consider moving forward.

Topic: 2.8 Contraception and perimenopause

P114 Contraceptive methods used by women aged 40 to 50

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Context
Although fertility decreases after age 35, perimenopausal women have a high probability of unplanned pregnancy. Given the risks of pregnancy and fetal chromosomal abnormalities in that age range, adequate contraception is needed until menopause. The choice of contraceptive method in women aged 40 to 50 is particularly challenging given the higher prevalence of comorbidities and the risks that this entails, which motivated the present investigation.

Objective
Come to know the contraceptive methods used by women aged 40 to 50 years and describe the type used according to their socio-economic status (SES).

Methods
A descriptive, cross-sectional observational study was conducted, carried out prospectively through a survey. The SES was categorized as low or high based on the studies considered, considering high SES if they had tertiary studies and low SES otherwise. The contraceptive methods used were categorized as oral contraceptives (ACO), prophylactics (PPX), intrauterine device (IUD), others or none. The difference between proportions in the categories was calculated by means of the chi2 test, considering $p < 0.05$ as significant.

Patient (s)
Women 40 to 50 years of age, non-carriers of surgical hysterectomy, menopause, thrombophilia, liver failure or oncological pathologies.

Intervention (s)
Self-administered survey in person or online, filled out anonymously.

Main outcome measure (s)
Type of contraceptive method used.

Result (s)
700 women were surveyed, with an average age 44.2 years (SD 3.21), mode 42 years, 50.1% married (255) or in a stable couple (168), 36.6% single and 13.3% divorced. 88% had work activity. The SES was high in 449 (64.1%) and low in 251 (35.9%).
The methods used were ACO in 346 cases (49.4%), PPX 115 (16.4%), IUD 101 (14.4%), another 43 (6.1%) and none 95 (13.6%).
The ACOs were used in 52.8% and 43.8% in the high and low SES respectively ($p = 0.026$), PPX 16.9% and 15.5% (p = NS), IUD 12.7% and 18, 3% ($p = 0.028$), other 5.6% and 7.2% (p = NS) and none 12.2% and 15.1% (p = NS).

Conclusions
The most commonly used contraceptive method was the ACO, followed by the PPX and the IUD in third place. Respondents with high SES used the ACOs to a greater extent, while those with low SES used the IUD more.

Topic: 2.9 Therapeutic uses of HC

P115 Influence of ethinylestradiol way of administration and progestins' type on ambulatory blood pressure monitoring in women on combined contraception

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Aim

Way of ethynylestradiol (EE) administration and progestins' type influence on ambulatory blood pressure monitoring (ABPM) in women on combined contraception (CC).

Patients and methods

54 non-smoking women without hypertension (age 19-45) were started on combined contraception (CC). Prior to CC initiation ABPM was carried out. ABPM was repeated after 6 month of CC.

Intervention

These women were divided according to way of EE administration and type of progestins' used. 43 women received EE oraly and 11 transdermaly. Drospirenon was administred orally to 17 women, dienogest to 13 women and gestodene to 10 ones. The control group consisted of 12 women with IUD contraception.

Results

Transdermal CC group showed statistically significant increase in minimal night diastolic blood pressure after 6 month of treatment (45.6 ±4.2mmHg vs 47.7±4.8 mmHg $p<0.03$). Oral application of CC showed no impact on APBM values. As far as type of progestin is concerned women on oral gestodene showed the reduction in heart rate(119,40 ± 9,08 vs 104,90 ± 11,28 /per min) ($p<0.03$). Drospirenon and dienogest showed no influence on ABPM parameters. There were no effect on ABPM in the control group.

Conclusion

Way of EE administration as well as type of progestin exerted nearly no influence on parameters measured during ABPM.

Topic: 2.9 Therapeutic uses of HC

P116 Damage reduction through etonogestrel implant in prevention of unplanned pregnancy in illicit drugs users in the Cracolândia, São Paulo

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Objective
To evaluate how contraceptive implant may reduce damage by preventing unplanned pregnancy in women users of illicit drugs.

Material
304 subdermal implants containing 68 mg etonogestrel inserted into women using illicit drugs in GRAVIUS project, voluntarily, by the Women's Health Reference Center, in central region of São Paulo, called Cracolândia, between March 2014 and June 2018. The average age of these women was 26.3 years. The criteria used as damage reduction were prevention of unplanned pregnancy, high-risk pregnancy, family damage (fate of children) and costs to public institutions.

Results
The facility of an unplanned pregnancy was observed due to the large number of pregnancies (3.2 pregnancies) and the non-use of any type of contraceptive method (36.4%) or inadequate use of the methods, such as condom (60.2%). and combined pill (9.3%). These are high risks pregnancies because they are women who have high rates of sexually transmitted diseases such as syphilis (20.1%) and HIV (4.8%), high incidence of abortions (17.2%), intrauterine fetal death (1.2%), prematurity (17.6%) and twinning (20% higher compared to the general population). Most of the fate of these children when they are born is to go to public shelters or most of the time, raised by their maternal grandparents. Preventing unplanned pregnancies for 300 women drug users has saved about U$ 250,000 a year for public institutions.

Conclusion
Prevention of unplanned pregnancy through subdermal implant in illicit drug users promotes reduction of maternal and fetal morbidity and mortality, family damage and public institutions, and should be promoted through structured programs, which aim helping the treatment of this population with drug addiction.

Topic: 2.10 Long lasting contraception

P117 Clinical aspects of contraceptive implants in prevention of unplanned pregnancy in illicit drug users in São Paulo

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Objective

To evaluate the clinical aspects of contraceptive implantation in the prevention of unplanned pregnancy in illicit drug users.

Material/Methods

Clinical aspects were observed regarding the insertion of the subdermal implant containing 68 mg of etonogestrel in 304 women using illicit drugs in the GRAVIUS project, voluntarily, by the Women's Health Reference Center, in the central region of São Paulo, Cracolândia, between March 2014 and June 2018. Joint action was taken with the RECOMEÇO project of the Reference Center for Alcohol, Tobacco and Other Drugs (CRATOD).

Results

215 patients (70.7%) returned at the end of this period due to joint action with the RECOMEÇO project. Bleeding pattern was revealed in 215 patients, as follows: 92 patients (42.8%) were amenorrhea, 49 (22.7%) infrequent bleeding, 40 (18.6%) monthly bleeding and 34 (15.8%) bleeding frequent/prolonged. Twenty extractions were performed: 5 (25%) were intoxicated, 3 (15%) due to abnormal uterine bleeding, 3 (15%) due to partner imposition, 2 (10%) due to local infection, 2 (10%) due to discomfort. 2 (10%) for headache and 1 (5%) for tubal ligation. Two more extractions were also performed because the patients were already pregnant at the time of insertion, and only one due to method failure in the second year of use, in which case due to constant use of thinner. In addition, 52 changes of implants overdue were performed so far, and 15 patients (28.8%) reported having ceased drug use.

Conclusion

An appropriate training of health workers that have to deal directly with female drug addict population, may provide proper orientation about contraceptive methods, specially about the subdermal implant, reducing its side effects, extraction, and allowing its mainly goal that is to reduce the unplanned pregnancy.

Topic: 2.10 Long lasting contraception

P119 Side effects and satisfaction evaluation of women using contraceptive implants for the prevention of unplanned pregnancy in medical training courses

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Objective
Evaluate side effects and women's satisfaction when using contraceptive implants for the prevention of unplanned pregnancy in medical training courses.

Methods
A retrospective study of 161 patients who following an explanatory lecture, spontaneously accepted to use the contraceptive measure of a 68mg subdermal implant of etonogestrel at the Women's Health Reference Center (Perola Byington Hospital), from September 2018 to June 2019, introduced by physicians with little experience in contraceptive insertion found in the training course stage. Data was collected by telephone after a 6-9 month period regarding possible complications, side effects and degree of contentment after the implant placing.

Results
Of the 161 women, the average age was 29 years old, mostly white (38.5%) and 47 (29.2%) have never previously gotten pregnant. After 6-9 months of insertion, the telephone call was answered by 92 (57.1%) patients, and most of them, 82 (89.1%), said they were well informed about the contraceptive method, as well as the implant insertion procedure, 34 women (37.0%) denied any indications or signs after the procedure. Of the women involved in the study, 44 (47.8%) stated they were very satisfied with the contraceptive implant whilst only 6 (6.5%) were unsatisfied. The main reasons for satisfaction amongst the women part in the research were safety (54.3%) and comfort provided by the method (59.8%). The causes of unsatisfaction were mainly attributed to irregular uterine bleeding (22.8%) and increased skin oil and acne (10.9%). About 32 (34.8%) women reported being with amenorrhea and 25 (27.2%) with infrequent bleeding pattern.

Conclusion
Most of the women who chose the contraceptive method have never gotten pregnant before. The explanation of the functioning of the implant and its possible side effects were related to the high content rates with the method, increasing its adherence. Safety and comfort are the reasons for the highest satisfaction by users while the occurrence of possible side effects may decrease adherence to the method or lead to early rejection and extraction of the implant.

Topic: 2.10 Long lasting contraception

P120 Epidemiology of women using the subdermal implant contraception for prevention of unplanned pregnancy in medical training courses

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Objective

Determine the epidemiological characteristics of women who chose the contraceptive implant for the prevention of unplanned pregnancy, and its possible insertion complications in the medical training course.

Methods

A retrospective study of 161 patients who following an explanatory lecture, spontaneously accepted to use the contraceptive measure of a 68 mg subdermal implant of etonogestrel at the Women's Health Reference Center (Perola Byington Hospital), from September 2018 to June 2019, introduced by physicians with little experience in contraceptive insertion found in the training course stage. Data was collected by telephone after a 6-9 month period regarding possible complications, side effects and degree of contentment after the implant placing.

Results

Of the 161 women, the average age was 29 years old, mostly white (38.5%), single (64.0%), only 19 (11.8%) had not completed high school and 92 (57.1%) are employed. Regarding sexual history, 47 (29.2%) have never gotten pregnant before and 15 (9.3%) did not use any contraceptive method. Condom was the most used method amongst the women present in the study (30.4%), while the combined pill was the most prevalent of the hormonal methods (28.0%). Only 6 (3.7%) patients used LARC. After 6-9 months of insertion, the telephone call was answered by 92 (57.1%) patients, and most of them, 82 (89.1%), said they were well informed about the contraceptive method, as well as the implant insertion procedure. Regarding the occurrence of local and transient implant-related symptoms, 49 (53.2%) reported hematoma at the insertion site and 27 (29.3%) reported pain. Both symptoms were present in 19 (20.7%) patients. Only 3 (3.3%) patients reported pruritus as another manifestation and 34 women (37.0%) denied any symptoms or signs after the procedure.

Conclusion

Most of the women who opted for the contraceptive method were young, had a job, and do not plan to get pregnant. However, many of them did not use any contraceptive method or use methods with low effectiveness rates. Therefore, it is important to recognize and seize opportunities for the prevention of unplanned pregnancies.

Topic: 3.1 Embryo implantation and development

P122 3D culture of human epithelial endometrial organoids: a new model for endometrial receptivity

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Context

Embryo implantation process involves complex interactions between the embryo and the maternal endometrium, disturbances in this bidirectional cross talk represent a reason for implantation failure. Due to the complexity of the mechanisms involved and the relative lack of information, embryo implantation has been defined the "black box" of assisted reproduction. Moreover, most of knowledge on mechanisms underlining human implantation derives from animal models, but they cannot always be translated to humans. Therefore, the development of an *in vitro* model allowing the opportunity to study the endometrial microenvironment and to investigate molecular mechanisms underlying this process, may be useful.

Objective

Validation of a human three-dimensional (3D) cell culture of epithelial endometrial organoids as a suitable *in vitro* model by investigating their responsiveness to hormonal treatments, able to induce the typical changes of the proliferative and secretory phases of the menstrual cycle.

Methods

Endometrial biopsies; 3D culture of epithelial endometrial organoids; Transmission Electron Microscopy (TEM); Scanning Electron Microscope (SEM); Gene expression by digital droplets PCR; western blotting and immunofluorescence.

Patient(s)

Caucasian women, in reproductive age (25-45 years old), undergoing hysteroscopy and endometrial biopsy for fertility workout (n=10), at the Obstetrics and Gynecology Unit, Siena University Hospital.

Result(s)

TEM and SEM analyses showed that organoids preserve glandular organization and ultrastructural characteristics; they retain the responsiveness to hormone treatment mimicking the *in vivo* glandular aspect and functions specific of the corresponding phase of the menstrual cycle, in particular we are able to *in vitro* mimic the structural endometrial modifications, as regard to pinopodes development, tipical of the implantation window. This was demonstrated by the analysis of Glycodelin A (GdA), a cycle-dependent marker of endometrial receptivity, that resulted to be expressed in cultured organoids with the same pattern detected in the endometrium *in vivo*, thus confirming the cycle-dependent modifications typical of this glycoprotein in epithelial endometrial cells.

Conclusions

This model could represent a valuable research tool to study implantation *in vitro*, and to test therapies for endometrial pathologies or implantation problems, allowing the possibility to build up patient-specific biobank resources.

Topic: 3.5 The infertile couple

P126 Single center retrospective evaluation of IVF in poor responders according to the Bologna criteria: prognosis and cost-effectiveness

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Context
The success of *in vitro* fertilization (IVF) depends on adequate follicle recruitment by using ovarian stimulation with gonadotrophins. Prevalence of poor ovarian response (POR) ranges from 9% to 24% in women undergoing ovarian stimulation for IVF and it is a growing phenomenon due to the increasing number of women delaying childbearing until the late 3rd-4th decade. The treatment of POR represents one of the main therapeutic challenges in modern reproductive medicine, considering the low live birth rates (6-8%) in this group of women.

Objective
To establish live birth rates in our cohort of poor ovarian responders according to the Bologna criteria and to analyze the cost effectiveness of IVF treatment in this subgroup of patients.

Methods
Retrospective analysis carried out at the Centre of Assisted Reproduction and Embryology, L. Sacco Hospital. We analysed women who underwent IVF treatment between January 2017 and December 2018 presenting a poor ovarian response according to Bologna criteria.

Patients
A total of 83 women undergoing their first *in vitro* fertilization (IVF) cycle who fulfil the Bologna criteria for poor response. The median age of our cohort of patients was 39 (3,6) years. All women were treated with the GnRH antagonist protocol. For ovarian stimulation 20 patients (24%) used Human Menopausal Gonadotrophin, 63 patients (76%) used recombinant FSH, with a median dosage of 200 IU per day. Human Chorionic gonadotrophin was given to trigger the final oocyte maturation when at least one leading follicle reached 18 mm in diameter. Fertilization was carried out *in vitro* either by conventional insemination or ICSI depending on semen parameters. Fresh embryo transfer was carried out 3-5 days after retrieval.

Results
The live birth rate in our cohort of Poor Ovarian Responders was 8.4%. Considering the cost of medications, oocyte retrieval and embryo-transfer, the cost of the IVF cycle for each patient was 5 416 Euro. Since we needed to treat 83 patient in order to achieve 7 live birth, our economic analyses showed a cost per live birth of 64 221 Euros.

Conclusions
Our retrospective data confirms that the Bologna criteria define a population with a low rate of success for IVF and, from a public health perspective, the opportunity to treat these women may be questioned.

Topic: 3.5 The infertile couple

P127 Risk assessment of reproductive health disorders in women after urgent gynecology interventions

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Context
Acute abdomen in gynecology is the main cause of urgent surgery. The frequency has not tended to decrease for a long time. The imperfection of diagnostic search and treatment tactics, the lack of effective rehabilitation measures, the recurrent nature of the pathology and the absence of pathogenetically justified antirecurrent therapy lead to serious long-term complications that adversely affect women's reproductive function.

Objective
Risk assessment of reproductive health disorders in women after urgent gynecology interventions.

Methods
The cases of reproductive health disorders during 52 urgent surgical interventions in women aged 18 to 40 years old were analyzed, which according to the available nosological pathology were divided into 4 groups: ovarian apoplexy (13), impaired tubal pregnancy (13), complicated cystoma (13) and unconfirmed gynecological pathology (13).

Results
The average age of women was 28.8± 7.2. Among previously gynecological diseases, 28% of cases were colpitis, bacterial vaginosis – 27%. Significant frequency of thyroid pathology (diffuse goiter – 11%, autoimmune thyroiditis – 14%) was noted, other somatic pathology met with approximately the same frequency ($p > 0.05$). Unauthorized early miscarriage was reported in 13%, unathorized late miscarriage in 12%, pregnancy terminated in 11%, infertility of tubal-peritoneal genesis in 8%.

Conclusions
Late complications such as the development of tubal obstructions, impaired vaginal microbiota, and hormonal imbalances adversely affect women's reproductive health, requring the revision of existing diagnostic and treatment algorithms and the creation of new prophylactic and rehabilitation programs aimed at improving fertility.

Topic: 3.5 The infertile couple

P131 Müllerian anomalies and infertility

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Context
Congenital Mullerian Anomalies represent a major concern because of the possible negative impact on women's health. The incidence of Mullerian anomalies among the general population is difficult to estimate. The most common forms of these anomalies include uterine septum, unicornuate uterus, bicornuate uterus and uterine didelphys. It is known that congenital uterine anomalies represent in many cases a cause for infertility and recurrent pregnancy loss. Many other obstetrical complications may link to the presence of Mullerian anomalies. In the present study we will present the most recent data about the impact of Mullerian anomalies on women's reproductive health.

Objective
The current study is designed to establish the link between Mullerian anomalies and infertility and to determine their impact on women's reproductive health.

Methods
A review of the literature was performed regarding the impact of Mullerian anomalies on women's reproductive health. The strategy implied using key words such as Mullerian anomalies, infertility, preterm birth with articles selection, narrative description of the obtained data and citation of the studied articles.

Results
The results show that women with Mullerian anomalies in addition to have a high risk for infertility, they also present an increased risk of first trimester miscarriage, preterm birth, fetal malpresentation at delivery, small for gestational age, preeclampsia and indication for caesarean delivery. It was shown that the risk of adverse pregnancy outcomes was increased in women with minor fusion defects (arcuate, septate and t-shaped) and also higher in women with major fusion defects (unicornuate, bicornuate and didelphys).

Conclusions
Mullerian anomalies are confirmed to have a great impact on women's reproductive health. These anomalies are associated both with infertility and with pregnancy complications. Taking into consideration that the incidence of these negative outcomes is depending on the specific subtypes of uterine anomalies, an adequate diagnosis and an appropriate therapeutic approach of these anomalies is essential.

Topic: 3.5 The infertile couple

P132 Cumulative live birth rate after *in vitro* fertilization: a single center analysis of 6546 treatment cycles

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Context
Live birth or pregnancy rates are commonly reported outcome measures in assisted reproduction. With the improvement of cryopreservation techniques and frequent implementation of freeze-all strategy the use of cumulative live birth rate (CLBR) is proving to be an accurate method to calculate the efficiency of *in vitro* fertilization or intracytoplasmic sperm injection (IVF/ICSI). Objective was to assess CLBR following infertility treatment with IVF/ICSI.

Methods
A total of 4787 women (6546 cycles), who underwent infertility treatment with assisted reproductive technologies (ART) between January 2009 and June 2019, were enrolled in the retrospective study. CLBR was defined as at least one live birth following one aspirated ART cycle, including all fresh and/or subsequent frozen-thawed embryo transfers (ETs), until one live birth occurs or all embryos are used.

Patients
All patients underwent ART treatment using autologous gametes. Patients lost to follow-up, oocyte freezing and genetic diagnostic cycles were excluded. Low and good prognosis patients were categorized according to POSEIDON criteria.
Interventions: none.
Main outcomes measure: cumulative live birth rate.

Results
At least one miscarriage (and no live birth) was registered by 358 (7.8%) women; 1310 (28.3%) patients had at least one live birth and 2952 (63.9%) – no pregnancies; 167 ETs were canceled due to ineligible embryo quality. The CLBR was significantly higher in younger women (<35 years): 35.0% (897/2566) versus 20.7% (413/1997) in patients ≥35 years, p<0.001. The CLBR rose with the increase of the number of retrieved oocytes (odds ratio (OR):1.85; 95% CI: 1.64-2.10) and good quality embryos of day 3 *in vitro* (OR:1.42; 95% CI: 1.34-1.50), p<0.001. Negative predictors for CLBR were cycle gonadotropin dose (OR:0.63; 95% CI: 0.59-0.66), and number of ETs per oocytes aspiration (OR:0.88; 95% CI: 0.82-0.94), p<0.001. The POSEIDON stratification was associated with CLBR, which was significant lower in group 2 (13.6%, OR 0.4, 95% CI 0.3-0.6, p<0.001) and group 3 (26.1%, OR 0.6, 95% CI 0.4-0.8, p=0.01) compared to good prognosis patients from POSEIDON group 1 (45.8%, 979/2139).

Conclusions
CLBR is an important index of success of IVF/ICSI treatment. Maternal age, cycle gonadotropin dose, number of retrieved oocytes and embryos available for subsequent ETs are directly associated with CLBR and could be applied for improvement of exciting models for prognosis of IVF/ICSI outcomes.

Topic: 3.5 The infertile couple

P133 Salpingectomy may decrease antral follicle count but not live birth rate of *in vitro* fertilization-embryo transfer women

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Context

Problems with fallopian tubes are one of the main reasons for women to undergo *in vitro* fertilization-embryo transfer (IVF-ET). A large proportion of women with ectopic pregnancy, fallopian tube obstruction and hydrosalpinx have had one or both fallopian tubes removed by salpingectomy. With advancing female age, declines in number and quality of oocytes are the primary reasons for decreasing IVF outcomes, especially in terms of live birth rates. Thus, it is important to understand how salpingectomy affects live birth rates for IVF patients of different ages.

Objective

To investigate how patient age and salpingectomy influenced ovarian reserve, ovarian response and pregnancy outcomes for infertile women undergoing IVF-ET.

Methods

A retrospective study.

Patient(s)

A total of 1737 patients that underwent IVF-ET treatment from January 1, 2013, to August 31, 2018, were included in this retrospective study. The patients were divided into two groups according to whether or not they had a previous history of salpingectomy. The salpingectomy (group A, 492 patients) and control groups (group B, 1245 patients) were then further divided into two subgroups according to patient age (age <35 years, and age 35-39 years).

Intervention(s)

None.

Main outcome measure(s)

Antral follicle counts and live birth rate.

Result(s)

In the salpingectomy group, antral follicle counts (AFC) were significantly lower for the subgroup aged 35 to 39 years compared with the control group. There were no significant differences in levels of basal follicle stimulation hormone (FSH), basal luteinizing hormone (LH), basal estradiol (E2), total Gn dose, duration of Gn, numbers of retrieved oocytes, fertilization rates, live birth rates, clinical pregnancy rates, miscarriage rates, ectopic pregnancy rates, or multiple pregnancy rates between the salpingectomy group and the control group (P>0.05).

Conclusions

In women from 35 to 39 years old, salpingectomy may decrease AFC significantly, which suggests a decrease in ovarian reserve. However, this decrease did not correspond to a significant change in the live birth rate. Moreover, bFSH, bLH, bE2, total Gn dose, duration of Gn, fertilization rates, and other pregnancy outcomes were similar between the salpingectomy group and the control group, regardless of patient age.

Topic: 3.6 Techniques in MAP

P134 Pregnancy, outcome and labor following assisted reproductive technologies based on the infertility factor

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Pregnant women after assisted reproductive technology (ART) are at high risk. The course of induced pregnancy is associated with a high incidence of obstetric and perinatal complications.

Objective

to study course and outcome of singleton pregnancies after ART (IVF and ET) according to the etiological factor of infertility.

Materials and methods

The course of pregnancy and labor was assessed in 78 women with singleton pregnancies after ART. Based on the etiological factor of infertility, these women were divided into clinical groups: group I (n=46) with tuboperitoneal infertility, group 2 (n=32) with endocrine infertility. The control group consisted of women with singleton natural pregnancies (n=32). All patients underwent clinical and laboratory examination, regulated by the protocol for the high-risk category of pregnant women. The main methods were ultrasound, dopplerometry, cardiotocography.

Results

The complicated course as a threatened abortion was more common after ART: 20 (43.5%) in tuboperitoneal infertility, 15 (46.5%) in endocrine infertility, 5 (15.6%) in controls, which was a significant difference ($p<0.05$). Threatened abortion was diagnosed in the early stages of gestation: 18 (39.1%) in tuboperitoneal infertility, 12 (37.5%) in endocrine factor, only 4 (12.5%) in controls. Fetal growth retardation was diagnosed in 40 (51.3%): group 1 in 18 (45%), group 2 in 22 (55%), and in 5 (15.6%) in controls. The frequency of preeclampsia was 26 (33.3%): 10 (38.5%) in tuboperitoneal factor, 16 (61.5%) in endocrine factor and 3 (12.5%) in controls ($p<0.05$). Caesarean section was performed in 57 (73.1%) patients after ART: 22 (38.6%) with tuboperitoneal factor, 35 (61.4%) with endocrine factor and 6 (18.8%) control patients. Elective surgery was performed in 50 (65.1%) after ART and in 5 (15.6%) in the control group. Urgent cesarean section in 7 (12.3%) after ART and 1 (3.1%) in controls. 16 (22.2%) children after ART and 7 (14.6%) control children were born with asphyxia. Asphyxia of newborns was significantly more common in children born from women after ART both with endocrine and tuboperitoneal factors ($p<0.05$).

Conclusions

In women after ART, obstetric and perinatal complications develop significantly more often.

Topic: 3.6 Techniques in MAP

P135 Increased chance of livebirth following use of connected ovulation test system: outcome results from randomised controlled trail

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Context
Natural conception requires intercourse during the fertile period which can be conveniently identified using ovulation tests. Most tests only measure lutenising hormone (LH). However, intercourse the day before the LH surge is associated with highest likelihood of pregnancy. Monitoring of estrogen enables identification of the wider fertile phase and is utilised by the Clearblue Connected Ovulation Test System. The system has an accessory App to store and compare results. A randomised controlled study found that its use doubled chances of conception in first cycle of use. Here we report the final outcome on livebirths.

Objective
To determine whether use of a connected ovulation test system increases the likelihood of livebirth.

Methods
Home based study of 844 volunteers, randomised 1:1 into the test or control arm. Volunteers participated for up to two full cycles. Volunteers conducted digital pregnancy tests (Clearblue), collected urine samples (hCG measurement, AutoDELFIA) and a diary of menses to determine pregnancy status. All pregnant volunteers were asked to complete a form on final outcome of pregnancy.

Patients
Women seeking to conceive aged 18-40 years. Exclusion criteria included; trying to conceive >6 months, diagnosis of PCOS, using fertility medications, currently pregnant, breast feeding, peri or post-menopausal, using contraception.

Intervention
Test group used the connected ovulation test system for up to 2 cycles. The control group were instructed not to use ovulation tests. Both groups were able to use other methods to time intercourse.

Main outcome measure
Livebirth Rate

Results
Data on conception rate has previously been published showing a total of 247 pregnancies, with higher conception rates in the test group (Cycle 1 Odds ratio 2.0, Cycle 1+2 Odds ratio 1.4). Final outcome data was available for 198 of these women, of whom 78% had a livebirth (Lost to follow-up; 17.2% Test group, 23% Control group). For cycle 1 conceptions, live birth rate was 16.4% for test group and 8.5% for control group; Odds ratio 2.12. For cycle 1+2 conceptions, live birth rate was 24.5% for test group and 17.5% for control group; Odds ratio 1.53.

Conclusions
The increased conception rate seen following use of a connected home ovulation test system does translate into an increased live birth rate. Users had at least double the chances of livebirth following one cycle of use, compared to not using an ovulation test.

Topic: 3.6 Techniques in MAP

P136 Modified natural cycle IVF

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Context
Many couples with infertility avoid IVF because treatment is stressful, costly to lots of patients and woman have medical contraindications.

Objective
The purpose is to suggest a way of infertility treatment, an option of IVF standard protocol, at comparable cost, with a lower emotional and drug burden.

Methods
Prospective clinical trial.

Patients
The study included 144 patients with infertility, aged up to 35 years inclusive, who were undergoing modified natural cycle IVF, with a regular menstrual cycle or confirmed ovulation, without male factor infertility.

Intervention
The patients underwent 3 attempts of modified natural cycle IVF, without stimulation of ovulation with the addition of ant-GnRH daily from the day when the maximum follicle reached a diameter of 14 mm. Human chorionic gonadotropin 5000 ME was used as the trigger of the final maturation of the oocytes.

Main outcome measure
Clinical pregnancy rate.

Results
The clinical pregnancy rate at the first attempt was 26% (n 37), at the second attempt – 17% (n 24), at the third attempt – 13% (n 19), the cumulative pregnancy rate for the 3 attempts was 56%, which is comparable to the frequency of clinical pregnancy on the initiated standard protocol.

Conclusions
Modified natural cycle IVF is an efficient and safe alternative to the standard protocol, and can be used in cases of reduced ovarian reserve, refusal of stimulation and medical contraindications.

Topic: 3.7 Ovulation induction

P137 Risk factors for no mature eggs in patients with diminished ovarian reserve

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Context

Women with low ovarian reserve present a higher risk for empty follicular syndrome (EFS) and the dose of medication and the trigger used may be other associated factors. The EFS is divided between genuine and false, with predictive factors. The frequency in cycles of ovarian hyperstimulation occurs in about 0.045 - 1.7%, and the most related causes are the diminished ovarian reserve, with frequencies from 4.25% to 7.2%, and advanced reproductive age. Some studies correlate the occurrence of EFS with a lower follicle count on the day of the trigger and lower levels of estradiol, others correlate LH and progesterone dosage on the day of the trigger as predictors of EFS, in an attempt to use alternatives to avoid EFS. The impact of not obtaining mature eggs at zero maturation rate and EFS is the same: cycle cancellation.

Objectives

Evaluate the risk factor for EFS or null maturation rate in women with low ovarian reserve.

Methods

retrospective cohort study

Patients

307 women underwent oocyte retrieval from October 2011 to July 2017. Intervention: none.

Main outcome measures

The women were classified as low ovarian reserve, due to FSH baseline > 10mUI/ml and antral follicle count (CFA) > 7. They were divided into 3 groups: I. maturation rate = 0 (n=17) or EFS (N=19); II. Maturity rate from 0 to 70% (n=75) and III. Maturation rate> 70% (n=196).

Results

The women used as trigger: hCG (65.47%), agonist GnRh (19.87%) and dual trigger (14.66%). Most of the women (90.67%) were submitted to the stimulus protocol with use of antagonist. The average age of women was 38.33 ±4.00 years. The mean maturation rate was 0.78 ±0.28. The baseline FSH, baseline LH was higher in group I than others ($p < 0.001$, $p = 0.036$ respectively). The EFS prevalence was 6,1%. The AMH and CFA was lower in group I than others groups ($p = 0.006$, $p<0.001$ respectively). The amount of FSH used in the stimulus was lower in women who did not have mature eggs, with $p = 0.003$. As a stimulus characteristic, women of group I had lower dosages of estradiol ($p<0.001$), fewer total follicles ($p< 0.001$), follicles larger than 16 mm ($p<0.001$), and fewer eggs retrieved ($p = 0.001$). The factors that correlated with the risk of developing EFS were using agonist GnRH ($p = 0.0044$), and total FSH dose used stimulus <1650 ($p=0.007$).

Conclusions

The use of agonist GnRH and the use of low doses of FSH during stimulation were associated with not obtaining mature eggs.

Topic: 3.8 Ovarian hyperstimulation

P138 Early injection of human chorionic gonadotropin in modified natural cycles can reduce premature ovulation and luteinization without adverse effect on IVF outcome in patients with advanced maternal age

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Context
Granulosa cell (GC) function rapidly declines after age 40 and therefore premature ovulation and luteinization is more frequently developed in modified natural IVF cycle despite gonadotropins and GnRH-antagonist supplementation.

Objective
This study was performed to investigate whether the early injection of human chorionic gonadotropin (hCG) in infertile patients with advanced maternal age (AMA) more than 40 years undergoing modified natural cycle IVF could prevent premature ovulation or luteinization without any adverse effect on IVF outcome.

Methods
Retrospective cohort study

Patients
One hundred twelve infertile patients over the age of 40 who underwent modified natural IVF were included in this study. Patients were excluded from this study if they were found to have any endocrine and metabolic disorders.

Intervention
This study included 123 consecutive modified natural IVF/ICSI cycles. A recombinant hCG (rhCG; Ovidrel, Merck Serono SA) of 250 μg was administered subcutaneously to induce follicular maturation when lead follicle reached a mean diameter of 16mm (early-hCG group, n=60) or when lead follicle reached a mean diameter of 17-18mm (control group, n=63) in our center between May 2018 and Oct 2019.

Main outcome measure
Premature ovulation or luteinization rate per cycle, progesterone levels on the day of hCG injection, IVF results and pregnancy outcome were compared between early-hCG and control groups.

Results
There were no significant differences in patient's characteristics between the early injection and control groups. Total dose and days of gonadotropins used were significantly fewer in the early-hCG group than in the control group ($P = 0.001$, $P < 0.001$, respectively). Serum progesterone (P) concentrations were significantly lower in the early-hCG group ($P < 0.001$). Premature ovulation or luteinization rate per cycle was significantly lower in the early-hCG group ($P = 0.017$). However, the mean numbers of mature oocytes and grade I or II embryos were similar between the two groups. Clinical pregnancy rate and embryo implantation rate were also comparable between the two groups.

Conclusion
Premature ovulation or luteinization in modified natural IVF cycles can be avoided without any adverse effect on IVF outcome by early injection of hCG in infertile patients with AMA over 40.

Topic: 3.9 Endometriosis and assisted reproduction

P138b A rare case of bilateral ruptured endometrioma mimicking ovarian malignancy

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Endometrioma involving ovaries are quite common. Rupture of ovarian endometrioma is quite uncommon, bilateral rupture rare. We came across a rare case of bilateral ruptured ovarian endometrioma mimicking ovarian malignancy. A 26 years old unmarried Indian girl from low socioeconomic group presented with lower abdominal pain 10 days duration and mild dysmenorrhea. Ultrasound showed bilateral complex vascular cyst. MRI showed bilateral complex haemorrhagic cyst with suspicion of mucinous cystadenocarcinoma. Serum CA125 and LDH were extremely high. Mild FDG uptake noted around periphery of bilateral adnexal mass lesion in PET scan raising concern of malignancy. On exploratory laparotomy, bilateral ruptured endometrioma with omental and peritoneal deposits and obliteration of pouch of doughlas with endometriotic deposits noted. Fertility preserving cyst excision done bilaterally. Patient was followed post operatively. Following a recurrence of 2 cm endometrioma after 18 months she was put on dienogest for 6-month period. Further follow up revealed complete regression and she conceived spontaneously in 3 months. CA 125, is a glycoprotein and a most useful tumour marker for epithelial ovarian malignancy. Even though it is generally believed that higher the value, the possibility of malignancy is high there are benign diseases with high value like endometrioma. Endometriosis rarely raise the value over 100IU, even though the highest value reported is 9300IU. Rupture of endometrioma may rapidly raise the CA125 value to very high levels. Raised and persistent value of CA125 does not necessarily indicate malignancy, may also be due to benign causes like endometrioma. This case was noted for the varied presentation and rarity.

Topic: 3.9 Endometriosis and assisted reproduction

P139 Endometriosis ovarian cysts and its impact on a woman's fertility

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The assessment of the ovarian reserve in women with endometriosis cysts, the sonographic picture of the condition of the operated ovaries, the level of anti-Muller hormone and FSH before and after treatment after 3 and 6 months and its impact on a woman's fertility.

One of the most common forms of genital endometriosis is an endometriotic lesion of the ovaries. There are three main areas of treatment: surgical, hormonal, combined. Surgical approach must reduce the risk of recurrence and preservation of the reproductive functions of women.

Study design

Under our observation there were 186 patients treated for reason of external genital endometriosis. Analysis of anamnestic data, clinical examination, gynecological examination, ultrasound examination, determined the level of CA 125, AMG, FSH. All examined patients in the first stage were performed surgery. We use the method of valesiana endometriotic cysts within the healthy tissue with minimal coagulation in the course of the wound. Hormonal studies were performed on 2-3 day of the menstrual cycle, after 3 and 6 months.

Results

Relapsing course of ovarian cysts diagnosed in 19 (33,3%) patients, of which 14 - surgical treatment in the anamnesis: in 35.7% of cases, resection of the ovary, at 64.3% - cystectomy. All patients with operative interventions on the ovaries in the anamnesis, the level of AMH was on the low end of normal, or were significantly below normal levels, averaging 2.5±0.5 ng/ml. follow-up study of hormonal status was performed in 49 (86%) patients. Were detected changes AMG by 12% (34 patients) compared with their performance before surgery. All patients' surgery was performed in a volume of cystectomy. In addition to cystectomy was performed lysis of adhesions (42,8%), endocoagulation of endometriosis (21.4 percent), myomectomy (10.7 per cent).

Conclusions

The status of the ovarian reserve in ovarian endometriotic cysts largely depends on the number and volume of surgical intervention; the Obtained results of hormonal studies allow to conclude that the most susceptible to intraoperative damage and significant marker of ovarian reserve is the AMH. The performed surgery at a gentle volume with maximum preservation of healthy tissue allows preserving the ovarian reserve and reproductive health of women

Topic: 3.9 Endometriosis and assisted reproduction

P141 Complex approach in managing the patients with endometriosis in Ukraine: role and place of the drug therapy. Experience exchange

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Endometriosis is a global problem and has a significant impact on the women's life quality.

Objective

To review the diagnosis and treatment options of endometriosis.

Methods

MEDLINE publications pertaining to the recurrence of endometriosis and its related yet unaddressed issues were analyzed. Review of the effects of post-operative drug therapy, recurrence rates, risk factors for recurrence and causes of recurrence.

Results

Recurrence rate after surgical interference is 21.5% during 2 years period and increased up to 40-50% during 5 years period. With the purpose of preventing the endometriosis recurrence, it is reasonable to apply combined approach – surgical methods and hormonal therapy. Total recurrence rate in 5 years period of advising post-operation treatment constituted 4% comparing to the 69% in treatment absence.

Conclusion

Treatment shall be conducted in accordance with the data of evidence-based medicine, with maximum performance of the drug therapy and abscond from the repeated surgical interference. Drug and surgical methodologies of endometriosis treatment shall be considered not as competitive, but combined, ones that increase the treatment effectiveness and improve the disease prognostication. To prevent endometriosis recurrence is recommended to conduct long-term hormonal therapy.

Keywords: endometriosis, surgical methodologies of endometriosis treatment, long-term hormonal therapy, reproductive health.

Topic: 3.9 Endometriosis and assisted reproduction

P142 Pregnancy outcome comparison of three controlled ovarian stimulation protocols for *in vitro* fertilization-embryo transfer in patients with diminished ovarian reserve after endometrioma cystectomy

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Context
Women with endometriosis and previous cystectomy may respond less well to gonadotropin stimulation, which results in fewer oocytes retrieved and poor pregnancy outcomes. This study involved an analysis of the effect of different controlled ovarian stimulation (COS) protocols on the clinical outcomes of *in vitro* fertilization-embryo transfer (IVF-ET) in women with diminished ovarian reserve (DOR) who underwent ovarian endometrioma cystectomy.

Objective
To provide an appropriate protocol for women with endometrioma cystectomy induced diminished ovarian reserve.

Methods
A retrospective study.

Patient(s)
342 patients that underwent IVF-ET treatment at the Beijing Obstetrics and Gynecology Hospital from January 1, 2013 to April 30, 2018 were included. The patients were distributed into three groups according to the COS protocols, namely prolonged GnRH-agonist (Group A, n=113), GnRH-antagonist (Group B, n=121), and long GnRH-agonist (Group C, n=108).

Intervention(s)
None.

Main outcome measure(s)
Clinical pregnancy rate and live birth rate.

Result(s)
There were no significant differences in the age, infertility duration, basic follicle stimulation hormone (FSH), luteinizing hormone (LH), or estradiol (E2) levels as well as other baseline characteristics among groups ($P>0.05$). The total gonadotrophin (Gn) dosage and duration tended to be less in the GnRH-antagonist group than in the others ($P<0.05$). No significant differences were found in the implantation rate and clinical pregnancy rate among the groups, but the prolonged GnRH-agonist group showed the highest rates. In addition, no significant differences were present in the number of retrieved oocytes, oocyte fertilization rate, live birth rate, abortion rate, ectopic pregnancy rate, or multiple pregnancy rate in the three groups ($P>0.05$)

Conclusions
For those DOR patients who had undergone ovarian endometriosis cystectomy, the prolonged GnRH-agonist protocol may achieve better clinical IVF-ET outcomes, but there were no significant differences from the other groups. The GnRH-antagonist protocol may reduce the cost and time of drug treatment.

Topic: 3.11 Endocrine disorders and medically assisted procreation

P142b Association of thyroid antibody positivity with adverse pregnancy outcomes in the first trimester after IVF programs.

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Context

Elevated levels of thyroid antibodies are associated with an increased risk of adverse pregnancy outcomes. Up to 20% of all pregnant women test positive for thyroid peroxidase antibodies (TPO-AB) or thyroglobulin antibodies while being euthyroid. Autoimmune anti-thyroid activity may increase the risk of spontaneous and recurrent pregnancy loss and preterm delivery even in euthyroid women.

Objective

To assess correlation of TPO-AB serum concentration with pregnancy outcomes in the first trimester for women after IVF programs.

Methods

Prospective longitudinal study. Statistical analysis was performed via MS Office Excel 2013, MedCalc, and Statistica 10.0.

Patients

388 women of reproductive age with primary infertility and pregnancy after IVF. Prior to IVF all patients were examined according to Belarusian national guidelines; additionally, serum concentration of TSH, free T4 and TPO-AB were assessed. Women were divided into 2 groups according to controlled ovarian stimulation protocols.

Interventions

In Group 1 (n=185) GnRH agonists protocol was applied; in Group 2 (n=203) GnRH antagonists protocol was used. Group 1 was divided into two subgroups: Subgroup 1a (n=29) - women with miscarriage in the first trimester; Subgroup 1b (n=156) - pregnancy lasted more than 12 weeks. The same scheme of subdivision was applied to Group 2: 29 women in Subgroup 2a and 174 patients in Subgroup 2b.

Results.

All patients included in the research were euthyroid. We found out that pre-IVF TPO-AB median serum levels were significantly higher in women with adverse pregnancy outcomes in the first trimester: Subgroup 1a vs Subgroup 1b - 402,8 IU/ml vs 16,2 IU/ml ($p<0,0001$); Subgroup 2a vs Subgroup 2b - 398,6 IU/ml vs 15,4 IU/ml ($p<0,0001$). Cut-off level of pre-IVF TPO-AB serum concentration for adverse pregnancy outcomes in the 1st trimester was established - 362,4 IU/ml (Se 89,66%; Sp 86,82%, $p<0,0001$; AUC 0,879).

Conclusions

Findings of the research demonstrate that elevated TPO-AB concentration in euthyroid women is associated with spontaneous miscarriage in the first trimester after IVF programs. Screening for TPO-AB prior to infertility treatment proves to be essential in order to improve pregnancy outcomes.

Topic: 3.13 Fertility preservation

P146 Impact of stepwise removal of ovarian tissue on ovarian function - animal study

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Objective

Removal of tissue is necessary for example for cryopreservation, now an established option for fertility preservation. Aim of this study was to investigate the impact of stepwise removing ovarian tissue on endocrine hormone levels reflecting ovarian function in rats.

Methods

Six groups, each consisting of six ten-week-old Sprague-Dawley rats. Five groups were partially or totally ovariectomized, another group used as control. Blood was obtained at the day of surgery (baseline) and thereafter every two weeks to assess serum hormones reflecting ovarian function, such as estradiol (E2), progesterone (P), follicle-stimulating hormone (FSH), anti-mullerian hormone (AMH), Inhibin B (INHB).

Surgeries in the groups; [%] of remaining total ovarian tissue: Group 1, n=6, non-ovariectomized [100% tissue]. Group 2, n=6, excising half of left ovary [75% tissue]. Group 3, n=6, excising left ovary [50% tissue]. Group 4, n=6, excising left ovary + half of right ovary [25% tissue]. Group 5, n=6, excising left ovary + three quarters of right ovary [12.5% tissue]. Group 6, n=6, bilateral ovariectomy [0% tissue]. All data were analyzed by repeated measures analysis of variance. If a significant overall difference was shown, the post hoc LSD test was used for further comparisons.

Results

During the 12 weeks group 4, 5 and 6 had higher FSH and lower AMH, INHB values compared to the control (group 1), but in group 4 the production of E2 and P was not significantly different from control. All ovarian function parameters completely stopped in group 5, i.e. without difference to the bilateral ovariectomized rats (group 6).

Conclusion

Our animal study confirms (what already is suggested from clinical studies) that removal of one ovary maintains the remaining ovarian tissue's potency for a normal production of ovarian hormones. However, to our knowledge for the first time it is demonstrated that even up to 75% of total ovarian tissue can be removed without impact on the production of E2 and P, which, if confirmed in women, would mean, that no hazardous hormone replacement therapy is needed, to avoid the negative consequences of hormonal depletion.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals' Ascent Plan, code: DFL20181401

Topic: 3.13 Fertility preservation

P147 Fertility outcomes in women with atypical endometrial hyperplasia and endometrial cancer grade I

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In available literature there is no generalized information about condition of the reproductive system of young women suffering from cancer, management tactics and the time to restore the implantation properties of the endometrium after the treatment.

Objective

Presentation of the first experience treatment of patients with endometrial cancer grade I or atypical endometrial hyperplasia directed to preserve oocytes or embryos.

Matherial and methods

77 women with endometrial carcinoma grade I or atypical endometrial hyperplasia, directed by oncologist for fertility preservation or pregnancy achievement. Among 28 women, performed IVF programs, 6 of them underwent ovulation stimulation, collection and cryopreservation of oocytes / embryos for the delayed reproductive function, after which the treatment of the underlying disease was started or continued. Twenty patients underwent an IVF program with embryo transfer in the "fresh cycle" after completing the treatment of cancer and achieving stable remission. 37 patients were excluded from the study due to different medical issues.

Results of the study

PCOS with severe endocrine-metabolic is diagnosed in 51% of cases, which makes it necessary to develop programs aimed at preserving reproductive material and treatment methods that reduce the risk of cancer recurrence. It was shown that the best results were obtained with preliminary cryopreservation programs in patients with normal ovarian reserve, also it has been demonstrated that IVF programs 3-4 months after completion of treatment are associated with better outcomes.

Conclusions

There is an increasing need for rehabilitation of the reproductive function of patients with atypical hyperplasia and stage I endometrial cancer, which makes this problem relevant. It is advisable to carry out preliminary cryopreservation of oocytes / embryos before treatment of the underlying disease due to the time spent on treatment, especially with initially reduced rates of ovarian reserve, fewer and worse quality of oocytes obtained after completion of treatment.

Topic: 3.13 Fertility preservation

P148 Reproductive potential of women with pathological endometrial processes

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Context

Undiagnosed endometrial pathology is one of the possible factors causing impairment of reproductive functioning.

Objective

Improvement of efficiency *in vitro* fertilization programs in women with infertility on the basis of retrospective determination of the main leading factors of implantation violation, causing complicated course of induced pregnancy.

Methods

There were performed retrospective analysis of histological picture of the endometrium pathology, reproductive anamnesis in patients whose pregnancy occurred after the use of "*in vitro*" fertilization (IVF) and has been terminated in the first trimester of gestation.

Patient(s)

There were examined 112 patients with tubal-peritoneal infertility factor.

Intervention(s)

All patients were performed hysteroscopy with histological and immunohistochemical analysis of the material.

Main outcome measure(s)

The following pathological states of the endometrium were revealed: chronic endometritis in 63 (56.25%) patients; endometrial polyps – in 21 (18.75%) patients; endometrial hyperplasia – in 5 (4.46%) patients; endometrial hypoplasia – in 11 (9.83%) patients; Asherman's syndrome in 7 (6.25%) patients; submucosal uterine fibroids in 5 (4.46%) patients.

Immunohistochemically chronic endometritis was found in endometrial polyps in 66.6% of patients, in synechiae – in 1.4% of patients, in endometrial hypoplasia – in 72.7% of patients, in submucosal uterine fibroids and hyperplastic processes – in half of patients.

Results

The average age of pregnant women was 34±3.1 years. In 38.75% of cases there were more than three IVF attempts in history, in 52.5% of observations the IVF program was performed for the first time. Gynecological diseases: pelvic inflammatory diseases of pelvic organs (70.9%), surgery on the pelvic organs (46.93%), intrauterine interventions (37.76%), cervical pathology (64.8%), mixed infections (46. 9%), ($p < 0.05$).

Conclusions

Impairment of fertility in women with pathological endometrial processes is an important problem, especially in women using assisted reproductive technologies. This requires the in-depth examination of patients to find out the probable causes of early reproductive loss and opens the prospect for further research.

Topic: 3.13 Fertility preservation

P149 Synergistic effects of N-Acetyl-L-Cysteine and taurine improve the protective efficacy of cryopreserved and thawed human ovarian tissue

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Objective

To investigate the protective efficacy of antioxidants N-Acetyl-L-Cysteine and taurine based on the currently-used human ovarian tissue cryopreservation and thawing protocol in our center, in order to preserve the viability of follicles and stroma cells, and improve the follicular development after thawing.

Methods

The currently-used cryopreservation and thawing protocol in our center was used as control group (Group C), with addition of 5 mM NAC (Group N) or 0.5 mM taurine (Group T), or with addition of 5 mM NAC and 0.5 mM taurine (Group N+T). Ovarian tissues from 33 cancer patients were assigned into the 4 groups randomly, 3 biopsies in each group. The biopsies were cryopreserved and thawed under the same routine procedure. After thawing, HE staining and Calcein-AM staining were conducted to evaluate the morphological characteristics and follicle viability; After *in vitro* culture for 4 days, we measured the 17β-estradiol (E2), anti-mullerian hormone (AMH) and glucose concentration in the culture medium; the cultured biopsies were used to detect the level of cellular reactive oxygen species (ROS) and total antioxidant capacity (TAC);

Results

All 4 groups obtained good preservation of follicle integrity and viability ($p > 0.05$), and Group N had higher proportion of developing follicles than Group C ($p < 0.05$). After 4 days culture, E2 concentration in culture medium has no significant difference in 4 groups. AMH concentration and glucose uptake level in Group N+T were markedly higher than Group C ($p < 0.05$). Group N and Group N+T had lower ROS levels than Group C, and correspondingly, the two groups has higher TAC levels than Group C ($p < 0.05$); ROS level in Group T was significantly lower than in Group C ($p < 0.05$), but comparison of TAC levels between Group C and Group T has no statistical difference.

Conclusions

The addition of NAC alone or taurine alone or combination of NAC and taurine could preserve the follicle integrity and viability. NAC and taurine could act synergistically, increasing the level of E2 and AMH and improving the overall activity of ovarian tissues after thawing, decreasing intracellular ROS production and enhancing antioxidant capability.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals'Ascent Plan, code: DFL20181401

Topic: 3.13 Fertility preservation

P150 First ovarian tissue bank in China: ten cases with ovarian tissue cryopreservation and transplantation

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Background

Ovarian tissue cryopreservation (OTC) is no longer considered as an experimental technology in developed countries such as Europe. OTC is the only fertility preservation option for hormone-sensitive tumors if chemoradiotherapy cannot be delayed and/or for prepubertal girls. OTC not only protects fertility, but also protects patients' ovarian function and prevents iatrogenic premature ovarian insufficiency (POI).

Objective

With international help, especially with German experts involved in the "FertiProtekt" Project, the first ovarian tissue bank of China was established in the Beijing Obstetrics and Gynecology Hospital, Capital Medical University. Aim is to report about the first ten transplantations successfully completed.

Methods

A retrospective descriptive study.

Results

From the 10 patients who undergone OTC and ovarian tissue transplantation (OTT), 5 of them were cervical cancer, 1 endometrial cancer, 1 breast cancer, 1 rectal cancer, 1 myelodysplastic syndrome, and 1 aplastic anemia. Average age at the time of OTC was 33.70 years, the average time from OTC to OTT was 15 months. After OTC, 6 cases underwent radiotherapy + chemotherapy, 2 radiotherapy, and 2 no chemoradiotherapy, but they underwent uterine and bilateral ovarian salpingectomy. The average number of transplanted pieces was 4.9, of remaining cryopreserved pieces 9.5. OTT position for 9 cases was on the right side and 1 case on both sides. 4 patients could get pregnancy in future, but 6 patients have no possibility of spontaneous reproduction because they have no uterus or the uterus was exposured to radiotherapy. The average time is 17.7 months from OTT to December 15th 2019. The average time of ovarian function restoration was 3.4 months after OTT. The average value of follicle stimulating hormone (FSH) was 4.44 IU/L before OCT, 65.423 IU/L before OTT, 17.03 IU/L 4 months after OTT. 1 year after OTT 100% of ovaries still alive. The ovarian function of the first case is still effective now after more than 3 years.

Conclusion

OTC and OTT is reliable and efficient performed in the first Chinese center. We hope that in the near future we will have a patient who will get a baby through this technique. We need more transplanted cases to supplement the global data on success rates and live birth rates using this technique.

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Funding: Beijing Municipal Administration of Hospitals' Ascent Plan, code: DFL20181401

Topic: 3.13 Fertility preservation

P151 Morphokinetic characteristic and euploidy rate of embryos derived from cryopreserved oocyte

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Context

Oocytes cryopreservation is an important part of assisted reproductive technologies that should ensure after warming the preservation not only cell morphological characteristics, but also their genetic apparatus stability. However, the meiotic spindle is sensitive to temperature fluctuations that can lead to unequal chromosome segregation during meiosis and as a consequence to cause the appearance of embryos aneuploidy after fertilization of cryopreserved oocyte.

Objective

The purpose of the study was to estimate the vitrification impact on oocyte fertilization rate, morphological characteristics and euploidy rates of human embryos derived from *in vitro* cryopreserved oocyte.

Methods

Oocytes were fertilized by ICSI then the derived embryos to day 5 were morphologicaly estimated by Gardner criteria and three to five trophectoderm cells were removed for pre-implantation genetic testing. Patient(s): The 29 ART cycles were retrospectively analyzed with the written consent of patients who underwent infertility treatment in an oocyte donation programme in “IGR MedicalCenter” from April 2018 toApril 2019. Intervention(s): All oocytes Fresh (n=469) were devided into two groups: fresh and virified. The fertilization rate, morphokinetic characteristics and aneuploidy rate of embryos obtained in both group were estimated.

Main outcome measure(s)

Oocytes vitrification does not impact fertilization and euploidy rates of human embryos.

Result(s)

The survival rate of vitrified oocytes was 96%. It has been shown that oocytes fertilization rate does not differ in both studied groups (83.1% (group1) vs 84% (group 2)). In the first group71.1% of blastocysts developed and only 38.5% of them corresponded to AA grade. Meanwhile, in the second group52.9% of the embryos reached the blastocyst stage of development and 55.8% of them corresponded to AA grade. There was no significant difference in the number of aneuploid embryos between the studied groups (54.1 vs 55.8% in groups1and 2, respectively).

Conclusions

Our data suggest that the oocyte cryopreservation by vitrification did not affect their fertilization rate and euploidy rate of the derived embryos. Despite the number of blastocyst was decreased in group 2, the number of embryos of an excellent quality was comparable with group 1.

Topic: 3.14 Autologue and heterologue donation

P151b Can nuclear transfer improve IVF outcome in women with elevated follicle stimulating hormone (FSH) level?

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Context

Currently, nuclear transfer (NT) techniques such as pronuclear transfer, maternal spindle transfer (MST) and the 1st polar body transfer (PBT1) to enucleated donor oocytes (DO) are being applied in some IVF clinics to prevent mitochondrial diseases transmission. However, there is a little known about NT effectiveness in women with hormonal disorders and poor ovarian reserve (POR).

Objective

To assess the effect of MST and PBT1 on embryo development and IVF outcome in women of different ages with high FSH level and POR.

Methods

Oocyte assessment, MST, PBT1 and sperm injection were performed using inverted microscope, micromanupulators, Oosight imaging and laser system. Blastocysts genetic testing was carried out by next generation sequencing. During controlled ovarian stimulation (COS) hormonal screening and follicle ultrasound monitoring were conducted.

Patients

31 women with high FSH level on the day 3 of menstrual cycle (15-23 mIU/ml) and low anti-mullerian hormone level (≤ 0.4 ng/ml) were divided in 2 groups, depending on their age. Group 1 included 17 women of advanced maternal age (39-43 years old), group 2 - 14 younger women aged 33-36 years. All women had ≥3 failed previous IVF cycles. In this IVF cycle, in total, 56 and 59 oocytes were obtained in groups 1 and 2 respectively. We used 243 DO of women aged 24-26 years.

Interventions

COS was conducted in protocol with GnRH antagonists. Each retrieved meiotic spindle from the patient's mature oocyte were placed in one enucleated DO (MST) and each polar body from this patient's oocyte was transferred to another enucleated DO (PBT1).

Main Outcome Mesuares

We compared fertilization rate of modified oocytes, embryo development, blastulation rate and aneuploidy rate between the groups with POR.

Results

Fertilization rate of reconstructed oocytes did not differ between 2 groups of patients (64 vs 68 %) and was comparable to this parameter in the previous IVF cycles. NT led to a 3-fold increase in the blastulation rate compared with previous attempts and promoted a decrease in the number of aneuploid embryos. However, in group 1 blastulation rate was lower (60 vs 71 %, $P<0.05$) and aneuploidy rate was higher (80 vs 47 %, $P<0.05$) than in group 2.

Conclusion

Simultaneous MST and PBT1 allow to double a number of oocytes with own nuclear DNA and improve embryo development at patients with POR and elevated FSH level. The better IVF outcome after oocyte reconstruction was observed at younger women.

Topic: 3.14 Autologue and heterologue donation

P152 Evaluation of uterine artery Doppler and estrogen milieu in oocyte donation pregnancies

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Context
Nowadays oocyte donation (OD) cycles represent 4.5% of all *in vitro* fertilisation cycles. While OD pregnancies face increased risks of obstetrical complications, especially pregnancy-induced hypertension and pre-eclampsia (PE), little is known about the physiology and the physiopathology of placentation.

Objective
Uterine perfusion in OD pregnancies could be different from spontaneous pregnancies and *in vitro* fertilisation pregnancies.

Methods and Patients
We performed prospective case-control study to analyse uterine arteries Doppler Pulsatility index (PI) and serum maternal 17 β – estradiol at 11+0-13+6 weeks' gestation. Four groups of singleton pregnancies were studied: 55 OD, 48 *in vitro* fertilization pregnancies with autologous oocytes from fresh cycle (Autologous IVF), 10 *in vitro* fertilization pregnancies with autologous oocytes from frozen cycle (Autologous – Frozen IVF) and 122 spontaneous pregnancies.

Results
Mean uterine artery PI and 17-β estradiol at 11-13+6 weeks were significantly lower in OD recipients compared to Spontaneous Pregnancies and Autologous IVF, either from fresh and frozen cycle.

Conclusion
Oocyte donation could have a significant impact on uterine arteries and hormonal milieu in the first trimester of pregnancy.

Topic: 3.15 MAP and ethics

P153 Surrogacy programs: medical, legal and ethical aspects

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Objective

To present the medical, legal and ethical points of view as they are formed in modern societies.

Methods – Patients

We present our experience after 15 years of continuous occupation with surrogacy programs worldwide enriched with the latest legal and medical data.

Main outcome – Conclusions

Nowadays we observe a rise in the number of surrogacy programs worldwide, due to medical and other reasons. Each day more couples use the – so called – "borrowed uterus" to complete their family. The huge progress of the IVF techniques allows better management and finally higher success rates. The rapid hearsay of the surrogacy programs raised questions about the morality and legality that had to be answered. Medical treatments are becoming more precise, with lower presence of side effects not only to the fetus but also to the surrogate mother. The development of the lab materials and techniques in combination to the new stimulation and transfer protocols have lead to increased take home baby ratios. On the other hand, legal systems recognize the need for detailed laws that will determine – without any doubt – the correlation between the intended parents, the family of the surrogate mother and the infant. Of course, all these have to meet the ethical code of each country and their people. We can see that there are major differentiations between countries that lead to uniqueness and on the accomplishment of a surrogacy program. This is the reason why many couples are achieving a program in another country than their residency that offers them a most friendly total experience. Greece has one of the most completed and progressive law system in this field and this is one of the explanations that a big amount of Greece's medical tourism dynamic refers to surrogate programs.

Topic: 4.1 Recurrent abortion

P154 Correlation between levels of homocysteine, anti-müllerian hormone and insulin resistance in PCOS patients with recurrent pregnancy loss

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Context

There are controversial opinions regarding the impact of hyperhomocysteinemia (HHcy) and insulin resistance in PCOS patients who experience Recurrent Pregnancy Loss (RPL). Nowadays the correlation between levels of Anti-Müllerian Hormone (AMH), homocysteine and insulin resistance have become the main subject of interest in PCOS patients for predicting Recurrent Pregnancy Loss.

Objective

Investigate the relationship between level of Homocysteine, anti-müllerian hormone and insulin resistance (IR) in PCOS patients with Recurrent Pregnancy Loss.

Methods-Patients

80 Georgian young women (<30 years) with PCOS were involved in the prospective study. The diagnosis of PCOS was based on the criteria of Rotterdam Consensus 2003.

Patients were divided into two groups: Group I-50 patients, who experienced two or more spontaneous abortions during the first trimester, and Group II-30 patients with live births in anamnesis (control group). PCOS patients with RPL were divided into two subgroups: subgroup A-with insulin resistance (n=28), and subgroup B-without insulin resistance (n=22). All patients underwent hormonal and US investigation from day 2 to 3 of menstrual cycle (AMH, homocysteine (Hcy), follicle-stimulating hormone, luteinizing hormone (LH), total testosterone (T), free testosterone (FT), sex hormone binding globulin (SHBG), ovarian volume and the number of antral follicles). Body mass index (BMI), homeostatic model assessment for insulin resistance (HOMA- IR), free androgen index (FAI) was calculated.

Results

Average Homocysteine (Hcy) level in PCOS patients with RPL (11.5±2.24μmol/l) was significantly higher than in controls (7.55 ± 2.45 μmol/l, $p<0.001$). Incidence of HHcy and IR in PCOS patients with RPL was 70% (n=35)
and 56% (n=28) respectively, which was significantly higher when compared to the controls (HHcy-54.3%; IR- 9.4% $p<0.001$).
HOMA-IR in PCOS patients with RPL was significantly higher compared with controls ($p<0.001$).

Average AMH level in PCOS patients with RPL and live births did not differ significantly. In the group of PCOS with RPL statistically significant positive correlation between Hcy and HOMA-IR, BMI, AMH and FT levels was found ($p<0.001$).

Conclusions

Serum homocysteine level is elevated in PCOS patients with RPL. This elevation is correlated with the degree of obesity, BMI, insulin resistance status, anti-müllerian hormone and androgen levels.

Topic: 4.1 Recurrent abortion

P155 Low HLA-G expression as a determinant in early reproductive losses

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Context

HLA-G is a molecule that was first known to confer protection to the fetus from destruction by the immune system of its mother, thus critically contributing to fetal–maternal tolerance due to inducing displacement of pro-inflammatory to Th1 cell-mediated response of Th2, has a positive influence on the process of implantation and placentation. HLA-G, the nonclassical class I molecule, is expressed as a membrane-bound protein but, unlike typical HLA-class I, is also expressed as a soluble protein with a unique C-terminus. Its expression is mainly restricted to the fetal–maternal interface on the extravillous cytotrophoblast, to placenta, amnion.

Objective

The purpose of this study is to investigate the HLA-G, HLA-DR, CD 56 and KIR2DL4 expression in chorionic villous among 2 groups with missed abortion: group 1 – with normal karyotype and group 2 – with polyploidy and to determine the polymorphism of KIR2DL4 gene in blood.

Methods

It was a prospective complex cohort study which consisted of 2 parts - genetics and pathomorphological investigation.

Patients

The first and second parts of study included 52 cases of abortion material from women with missed abortion: 27 with fetal normal karyotype and 25 with fetal polyploidy.

Interventions

Criteria of inclusion: abortive material from two groups of women residing in North-West region of Russia either with missed abortion; 6-12 weeks gestational age, singleton pregnancy, cytogenetic of chorionic villous was obligatorily - normal fetal karyotype and polyploidy of fetus. Pathomorophological investigation included H&E stain, immunohistochemistry (IHC) and confocal laser scanning microscopy (CLSM).

Main outcome measures and results

The spreading by genotypes of this gene was not statistically different among 2 groups. During pathomorphological investigations by IHC was counted the average relative area of HLA-G expression in trophoblast. Expression of HLA-G the most verified in syncytiotrophoblast, cytotrophoblast, extravillious area contrary to expression of HLA-DR and CD56 which were verified in endometrial tissue. The average relative area of HLA-DR and CD56 expression were lower in endometrium of the group with normal karyotype.

Conclusion

This results suggest the role of HLA G for the progression in early reproductive losses. Low expression of HLA-G is associated with pregnancy complications and can be one of the reason of spontaneous abortion (such as RPL).

Topic: 4.1 Recurrent abortion

P157 Assessment of the gynecological and psychological status of the patients after spontaneous abortion in the first trimester

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Purpose

This study deals with gynecological and psychological status of patients with spontaneous abortion in the first trimester.

Materials and methods

The study population consisted of 200 patients aged 23 to 41 years, divided into two groups. The main group consisted of 100 patients hospitalized after a miscarriage in the first trimester, the control group consisted of 100 pregnant women without threatened abortion. All patients underwent a complete clinical and laboratory examination, collection and evaluation of medical history data, symptomatic treatment. The study and analysis of psychological status was carried out using psychological screening diagnostics, which included: questionnaires, questionnaires, tests, projective techniques that identify trends in somatic state and the threat of miscarriage; questionnaires and projective tests that reveal the formation of readiness for childbirth and motherhood - picture tests "I and my baby"; "Me and my mother in childhood"; "Double drawing of man"; Maternal ontogenesis questionnaire; Questionnaire regarding his body; Copy test (Lazarus); MMPI (Minnesota Minnesota Personal Profile) - Scale No. 5; Questionnaire on social adaptation and stress tolerance of Holmes Rey); WHQ (Women's Health Questionnaire).

Results

According to the results of our study, the most important factors in early termination of pregnancy are: age up to 25 years, smoking, early onset of sexual activity, menstrual disorders, inflammatory diseases of the uterus and appendages, bacterial and viral associations, ovarian dysfunction or endometritis in history, repeated abortions, aggravated somatic history (hypertension, iron deficiency anemia, diseases of the thyroid gland), violation of the ontogenesis of the maternal sphere. Psychological studies have shown that patients with miscarriage often have conflicting relationships with their mother, they are also characterized by an intrapersonal conflict, deep internal dissatisfaction, manifested in inadequate self-esteem, bearing the character of psychological protection, full of conflict and anxious self-presentation as a mother. In this regard, it requires not only medical

Topic: 4.1 Recurrent abortion

P158 Evaluation of the endocrinological status of patients with spontaneous abortion in the first trimester

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but also psychological assistance, which is aimed at psychological correction and psychotherapy of the sources of internal conflict in the maternal sphere, which is the cause of the formation of a destructive image of motherhood. The negative experience of a failed pregnancy greatly increases the level of anxiety and has a negative effect on the course of subsequent pregnancies, which can lead to repeated episodes of spontaneous termination. The data obtained suggest the necessity, in addition to clinical, pathogenetic treatment and psychological support of women with a terminated pregnancy in history during the preparation process and during the new pregnancy, which is the subject of our study. Comprehensive treatment of the causes of miscarriage using assessment and correction of psychological status is a pronounced factor in reducing early reproductive losses.

Conclusion

Comprehensive treatment and prevention of causes of miscarriage using the correction of psychological status is a pronounced factor in reducing early reproductive losses.

Topic: 4.1 Recurrent abortion

P159 Association of Infertility with recurrent Pregnancy Loss (RPL) in Georgia

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Context
In some cases infertility and RPL have a common etiological background and treatment strategy. Often Infertility is a result of miscarriage.

Objective
Detection of frequency and character of primary and secondary infertility in couples with RPL. Revealing the association between infertility and RPL, determined by various etiological factors.

Methods and patients
Comprehensive investigation of RPL have been conducted in 281 couples (aged 21-41yy.), who applied to our center in 2016-19yy. In all couples family and personal anamnesis, anatomic, hormonal, immunological, genetic and thrombophilic causes of RPL have been studied. For further analyzes 140 couples have been selected with detected etiological factors of RPL. ART was not used in any case.

Results
Primary infertility before RPL was detected in 46 couples from 140 (32,8%) and secondary infertility (post RPL) – in 75 couples (53,6%). The association between primary infertility and RPL determined by endocrine factors has been revealed. Secondary infertility was not associated with etiological factors of RPL and mainly was tied with psychological or medical complications of miscarriages. Most common reasons of secondary infertility after RPL were: hyperprolactinemia, anovulation, PID, endometrial polyps and adhesions. Male partners with balanced chromosomal translocations were sub-fertile. After timely and comprehensive diagnosis and treatment from 140 couples 82 women (58,5%) delivered healthy babies and 40 women (28,6%) are still pregnant (II-III trimester).

Conclusions
Women with infertility of endocrine genesis represent the high risk-group of pregnancy loss (PL). Prevention of PL requires comprehensive correction of hormonal parameters before conception and intensive antenatal care. RPL is high risk factor for development of secondary infertility in women. Prevention and effective treatment of secondary infertility requires timely applying to psychologist and physician specialist to minimize stress and adverse medical results of miscariage.

Topic: 4.2 Extra-uterine pregnancy

P161 Conservative management of cervical ectopic pregnancy

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Context

One of the rare types of ectopic pregnancy is the cervical pregnancy – when the gestational sac is implanted in the endocervix. For 20 years there is significant increase of the ectopic pregnancies - from 3 ‰ to 19.7 ‰ of all pregnancies. The incidence of cervical ones is reported to be less than 0.1% of all extrauterine pregnancies. Some of the risk factors concerned with the rise of these events are the widespread use of intrauterine devices, more common pelvic inflammatory disease, rising rates of abortions, artificial fertilization, endometriosis, higher age, race, etc.

The cervical pregnancies are cases to be followed with caution for severe life-threatening bleeding due to penetration of the cervical walls up to cervical blood vessels. This may lead to hysterectomy as last step for saving the patient's life.

Patient

The reported case is a 33-year-old woman with a history of 2 previous Caesarean sections. This pregnancy was not planned, therefore the patient informs about intake of morning after pill 13 hours after the intercourse. She presents at 5th week of gestation with gestational sac in the cervical canal. A trial for medical abortion was tried with Mifepriston 600 mg orally + Misoprostol 400 μg orally 48 hours later. Serum beta human chorionic gonadotropin (hCG) was measured after one day showing result of 15 000 mIU/ ml. Later conservative treatment with Methotrexate intravenously was given on day 1, 3, 5, with a continuous follow-up of the beta hCG and ultrasound scans. The transvaginal scans at day 6 of the administration of Methotrexate revealed regular gestational sac with embryo with fetal heart beats in the cervical canal. This leaded the need of curettage followed by intracervical balloon tamponade of the cervix. The next day transvaginal scan proved empty uterine cavity and cervical canal. The levels of the serum beta hCG slowly dropped down to normal within 4 weeks.

Conclusions

Despite the low rates of the cervical pregnancy, the incidence of ectopic pregnancies nowadays are rising. This initiates the need of proper management and diagnose in order to safe the fertility and exclude unnecessary hysterectomies.

Topic: 4.2 Extra-uterine pregnancy

P162 Could ovarian hyperstimulation and high levels of progesterone be a risk factor for an ectopic pregnancy in ART?

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Context
The ectopic pregnancy (EP) rate has been reported higher after assisted reproductive technology (ART) than after a spontaneous conception. The factors associated with abnormal implantation are widely discussed and not completely clear.

Objective
The aim of the study was to determine the risk factors associated with EP in patients undergoing *in vitro* fertilization treatment.

Methods, patients, interventions and main outcome measures
The present study was an observational retrospective trial, performed in a private IVF clinic. It encompassed 366 women who have undergone *in vitro* fertilization treatment: stimulated cycles with fresh embryo transfers (STIM ET) and hormone replacement therapy with frozen embryo transfers (Fr ET). Four features were evaluated: endometrial thickness at the day of ET, stage of the embryos transferred – cleavage stage (day 3) or blastocyst stage (day 5), the progesterone level on the day of hCG in stimulated cycles, ovarian hyperstimulation (OHS). The primary outcome measure was a development of EP. Logistic regression was performed to utilize the significance of the numbers.

Results
At total of 366 Fresh ET or Fr ET cycles were compared, where 41 were with EP and 325 with an intrauterine pregnancy. We detected that thin endometrium could be risky for developing EP, but only in stimulated cycles (endometrium in STIM ET and EP = 10.7 mm versus STIM ET and no EP = 11.8 mm; p = 0.029). In contrast, with Fr ET cycles, the size of the lining was not important for the occurrence of EP (Fr ET and EP = 10.6 mm versus Fr ET and No EP = 11.14 mm; p = 0.2). This comparison emphasizes the observation that EP is more often detected in stimulated than in frozen cycles (61.98 % versus 39.02%; p = 0.04). Something more, most of the EP are resulted after a transfer of blastocyst stage embryos but only in stimulated cycles (EP rate 52% versus 21%, p = 0.0009). Also, we have established that high level of Progesterone on the day of hCG trigger could contribute for an ectopic embryo implantation (progesterone in STIM ET and EP = 1.05 ng/ml versus STIM ET and no EP = 0.59 ng/ml; p = 0.0014).

Conclusions
This study shows an increased risk of an ectopic pregnancy in stimulated ET cycles than in frozen ET. Endometrium thickness over 12 mm and progesterone level under 1 ng/ml could be a preventive measure for EP development.

Key words: ectopic pregnancy, ART, endometrial thickness, progesterone, ovarian hyperstimulation

Topic: 4.2 Extra-uterine pregnancy

P163 Ectopic pregnancy in distal Fallopian tube remnant after ipsilateral “salpingectomy” – an admonishing case report

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Introduction

Tubal ectopic pregnancy (TEP) accounts for 1.0-1.5% of all pregnancies and around 95% of ectopic pregnancies (EP). Tubal-preserving salpingotomy is the “gold standard” for TEP treatment. Complete tubal removal (salpingectomy) is indicated if the tube is irreversibly damaged or on patients request.

Case Report

A 26 yo, G4P0, BMI 23, with known uterus duplex, presented with acute abdomen at 6+2 weeks of gestation. The serum hCG was 1995 U/ml. On ultrasound, an EP adjacent to the right ovary was suspected. During emergent laparoscopy, a TEP – in absence of the proximal ¾ of the right tube – was removed from the distal tubal remnant (DTR) (Fig.1b-c). Following surgery the patient was discharged home on the 2nd postoperative day. The histology confirmed the presence of chorionic villi in the DTR (Fig.1d). Apart of the unusual EP localization, the patient’s history had three unique aspects. Firstly, after two spontaneous miscarriages (18 and 15 months earlier) she had a TEP on the right side (12 months ago), which was treated with “partial salpingectomy” (in fact, subtotal proximal salpingectomy). Secondly, the patient was carrier of a BRCA-1 mutation and four of her relatives died from breast and/or ovarian cancer. Therefore, she planned a risk-reducing salpingectomy after completion of childbearing. Thirdly, six months following TEP the patient underwent a laparoscopy and dye test with coagulation of peritoneal endometriosis, confirmation of uterus duplex and evidence of left tubal patency. Peculiarly, the DTR on the right side was documented (Fig.1a), though not removed.

Discussion

During two consecutive surgeries, the nonfunctional DTR was left despite known BRCA-1 mutation. Since high-grade serous ovarian cancer (HGSOC) can originate from the Fallopian tube, salpingectomy with post-reproductive ovariectomy is a considerable option in patients with BRCA-1/-2 mutations. If the contralateral tube remains patent, the risk of EP in the ipsilateral DTR is rare but realistic (roughly 35 reported cases). Such challenging EP is completely avoidable and can be considered “iatrogenic”.

Conclusion

There is no rationale for partial unilateral salpingectomy. If indicated, complete tubal removal prevents unusual EP localization and can be part of risk reduction strategy in high-risk patients. Additionally, this case affirms maintenance of spontaneous fertility in presence of uterus duplex combined with only one functional tube.

Topic: 4.2 Extra-uterine pregnancy

P164 The level of homocysteine, folic acid use of the dose-dependent methotrexate treatment extra-uterine pregnancy

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Objectives

The aim of this study was to determine the levels of homocysteine, folic acid, in patients with progressive ectopic pregnancy, treated with different doses of methotrexate.

Materials and methods

Group I (30 women) included patients with an ectopic pregnancy who were treated intramuscularly with methotrexate (100-75 mg) once, and patients of group II (30 women) received additional 100-75 mg of methotrexate after 7 days. The control group consisted of 30 healthy women.

Results of the study

Twice administration of methotrexate at both 7 and 30 days diagnosed significant increase in the level of homocysteine, enzymesaspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in the blood plasma. The level of folic acid on the background of the use of methotrexate is significantly decreased. Once-daily use of methotrexate has no cytolytic effect on the liver cells; its level is increased with the use of the dose-dependent methotrexate.

Conclusions

Patients with progressive ectopic pregnancy should be offered conservative drug treatment, which will preserve the reproductive function of women in the future. In women who underwent medical treatment with cytostatic it is recommended that the obligatory control of the biochemical parameters of blood and the determination of homocysteine, folic acid as factors that are clinically significant and may indicate a violation of the folate exchange and recommended that folic acid be obtained throughout the period of the preparation for the next pregnancy to normalize laboratory parameters.

Topic: 4.3 Prenatal diagnosis

P165 Envoy screening and diagnosis of the fetal profile

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The first French recommendations framing the practice of obstetric ultrasound date from 2005. The analysis of the fetal face was then limited to the "nose-mouth" section examining the nostrils as well as the continuity of the upper lip. The purpose of this cut is to detect cleft lips. The congenital pathology of the cleft lip meets certain screening criteria for large populations as defined by the World Health Organization (WHO) and is still therefore part of the list of required items.
In 2016, the revision of these national recommendations added several items to the 2005 version. The acquisition and so-called subjective analysis of the sagittal profile is part of this new text.
Morphological examination of the fetus and screening for malformations is the most spectacular - and most publicized - aspect of obstetric ultrasound. But it is certainly not the most useful or the most profitable compared to other decisive contributions of this technique for prenatal surveillance (vitality and fetal growth, amniotic fluid, presentation, placental insertion, twin pregnancies...). Indeed, morphological anomalies only affect 1 to 2% of pregnancies and, for a large part of them, screening has no objective utility: minor anomalies or moderate malformations whose in utero diagnosis does not change the obstetric care. There are objective markers of normality, some measurable, whose interest is obvious. However, in the case of the fetal profile, we will be very careful in the subjective assessment of the quality of a profile or the aesthetics of a 3D reconstruction of the face. Interindividual or ethnic variations can be significant, a displacement of a few millimeters from the section plane - or its orientation - can make a chin "leaky" or a forehead "bulging". The diagnosis of an abnormal facies will only be made with caution, except in a caricatural situation or in addition to objective anomalies, remembering that very often the face is a reflection of the brain.
The present review outpoints objective 2D ultrasound criteria of the normal fetal profil and proposes analytic criteria for the diagnosis of anomalies.

Topic: 4.3 Prenatal diagnosis

P166 Pre- and post-natal diagnosis of 22q11 deletion syndrome associated with cardiac and extracardiac manifestations – a case report

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The clinical spectrum of the DiGeorge syndrome has been fairly described using the CATCH-22 acronym, which includes Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia, all of these resulting from 22q11 deletions. We report the case of prenatal diagnosis of DiGeorge syndrome associated with right aortic arch, right ductus arteriosus, membranous ventricular septal defect and thymus aplasia of the fetus. A 36 years old gravida, whose fetus develops at 17 weeks of gestation bilateral hydronephrosis, with a strong suspicion of fetal thymic hypoplasia. At 22 weeks of gestation, the presence of the mentioned cardiac and extracardiac abnormalities was confirmed. An amniocentesis and FISH tests were conducted and diagnosed the DiGeorge syndrome. The particularity of the case is that we found multiple abnormalities that are rarely associated with this syndrome. This diagnosis should be suspicioned anytime the prenatal ultrasound examination image is suggestive for defects such as those found in our case.

Topic: 4.3 Prenatal diagnosis

P167 Fetus as our patient: pattern of referral of antenatally diagnosed fetal malformations and their outcome

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Objective
To review the pattern of referral for antenatally diagnosed fetal malformations and their fetal outcome in a tertiary care institution

Methods
This prospective study included pregnant women, between 12-36 weeks of gestation, who were referred to the Division of Maternal Fetal Medicine, AIIMS, New Delhi during August 2018 to January 2019

Results
A total of 347 pregnant women with fetuses having major malformations (n=272) and soft markers (n = 75) on prenatal ultrasound screening were referred to our tertiary care referral centre for further management. Majority of the fetuses with major anomalies were found among women aged 30–34 years and most were detected during the routine level II scan. The major anomalies were most common in the cardiovascular system (n=108; 31.1%), followed by the central nervous system (n=54; 15.5%) and the genito-urinary tract (n=43; 12.3%). 96 (27.6%) patients underwent medical termination of pregnancy.

Conclusion
Early diagnosis of fetal abnormalities is now routinely possible with recent advances in screening techniques such as 3D high-resolution fetal ultrasound, fetal magnetic resonance imaging and fetal echocardiography. It is essential to have detailed information about the incidence of fetal malformations, means of detection and evaluation, scope of possible in-utero fetal intervention, timing and mode of delivery, management and role of postnatal interventions and long-term sequelae. Apart from arranging for delivery at a tertiary care hospital in certain antenatally diagnosed fetal malformations where immediate care of newborn is required, there is a lot of scope for new in-utero invasive therapies for the unborn patient.

Topic: 4.4 Prenatal medicine

P168 Incidence of pregnancy and perinatal risk in patients under 15 years in Regional Clinical Hospital of Concepción, Chile

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Introduction

Teen pregnancy has shown a decline in our country in recent years, within this group, children under 15 years of age have stood out worldwide as a group with greater maternal and neonatal morbidity and mortality in relation to the rest. Our goal is to characterize this last group in our center to see if it is associated with more maternal and fetal morbidity and mortality.

Material and Methods

Cross-sectional descriptive study of births in women 15 years of age or younger who were treated at Guillermo Grant Benavente Regional Hospital between July 2016 to July 2019. A review of the books of the delivery unit of said center was made, compiling the data obtained in an Excel spreadsheet. A univariate analysis was performed for qualitative and quantitative variables. The Stata V.14 program was used.

Results

A total of 20 women under 15 years old had their birth at the Regional Hospital of Concepcion during the three years of review corresponding to 0.2% of total births. The average age was 13.8 (0.52%) years and 75% of these patients was the first pregnancy. The average gestational age was 39 + 2 weeks (1.18). Within the study group, 20% had perineal tears, 45% had an episiotomy and 5% had both conditions; 85% had vaginal delivery and 15% caesarean section. The pathology with the highest prevalence was fetal growth restriction in 25% of patients.

Conclusions

Births in adolescent women under 15 represent a low percentage of our center's total births, which is related to the reality of our country that showed a decrease in teenage pregnancies. There was no higher rate of caesarean section or prematurity of newborns in this group. The most prevalent pathology was fetal growth restriction affecting a quarter of pregnancies. Simultaneously, a project for the prevention of second pregnancy in adolescents is being carried out simultaneously, which would be interesting to correlate in the future. We suggest continuing to study this group to have a greater number of patients and to be able to carry out a study considering also the neonatal aspects.

Topic: 4.4 Prenatal medicine

P169 Pregnancy follow-up in primary hyperparathyroidism – case presentation

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Introduction

The evolution of spontaneous pregnancy in a maternal system with known hypercalcaemia and hyperparathyroidism, is a rare and difficult task in respect to the safety of the fetal development.

Objectives

Our work presents the evolution in preconception, pregnancy and postpartum period of a 28 year female, previous known with primary hyperparathyroidism.

Material and Method

We are presenting the case of a 28 year old female, diagnosed in February 2016 with symptomatic primary hyperparathyroidism.
Clinical characteristics: anamnestic increased heart rate episodes, most frequently during night sleep period.
Complete ultrasound evaluation was performed with a Hitachi Preirus machine, with a linear multifrequency probe, using conventional, Color Doppler and strain elastography technique: visualization of left inferior parathyroid.
Scintigraphy showed an image of minimum overactive left inferior parathyroid gland
Complete biochemical profile was performed.
The recommendation at diagnostic was surgical removal of the parathyroid gland.
Spontaneous evolution: despite treatment indication, the patient did not pursue to surgery, the biochemical markers increased (August 2016) with proportional increase of the parathyroid volume (ultrasound evaluation). Unplanned pregnancy appeared in December 2016.
Monthly biochemical follow up of the maternal calcemia were performed.
Pregnancy outcome: natural delivery, week 38, male, neonatal Apgar score 10.
Maternal outcome: parathyroidectomy in the postpartum period. Fluctuant hypoparathyroidism – initial functional, late onset definitive - did develop.
Neonate outcome: active screening for functional hypoparathyroidism in the neonate was performed.

Conclusion

The present case did show a rare case on unplanned pregnancy in a treated symptomatic primary hyperparathyroidism. Treatment options are limited during the pregnancy course; watchful waiting of the maternal levels of calcemia and dietary counseling are the only tools available. Emergency parathyroidectomy if the calcium levels exceed the safety threshold, are the only available interventional tools.

Topic: 4.4 Prenatal medicine

P170 Knowledge about the side effects of drugs and their preventive role against teratogenic effect on pregnancies

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Introduction

Many epidemiological studies on knowledge of medication use during pregnancy have been conducted all over the World. Some of them have shown that women still have poor knowledge and lack of concern about some health risks in pregnancy. Studies of this kind haven't been conducted in Kosovo before.

This paper attempts to evaluate the general knowledge about the side effects of drugs, attitudes and medication use during pregnancy. The purpose of this research was to assess the quality level of health services from the perspective of the recipients of these services.

Methodology

A qualitative, cross-sectional survey was conducted to 150 pregnant woman. A self-administered questionnaire included questions on demographic characteristics, knowledge about drug use and resistance, attitudes and behaviors towards drug use, and sources of information. The sample used in this study was selected by simple random sampling method. The data were analyzed and compared by using SPSS program.

Main outcome measure

To assess the state of knowledge of the pregnant women about medicines, to consider and evaluate the use of medications during pregnancy, to analyze the role of the health professional as part of the socio-medical service in providing knowledge of drugs in the care of pregnant women.

Results

A total of 134 patients filled the questionnaire properly. The study proves that pregnant women's knowledge about the side effects of the drugs is superficial, they know that the drugs can have side effects but lack specific knowledge and their answers are incorrect or incomplete. Respondents with higher education, employed, with a family member working in the health care sector were more likely to know about the drugs side effects and teratogeneses. Approximately 82% of women reported taking at least 1 medication, the most frequently used drugs were paracetamol and vitamins (83.6%). Women indicated inadequate provision of drug-related information from physician and pharmacist.

Conclusions

The study indicates patients need for more information, the information available is not sufficient and they need more when it comes to drugs during pregnancy and teratogenic effects. Educational programs for women about medication use are important to increase their knowledge of the potential risks to the pregnant women and the unborn child in order to reduce self-medication.

Key words

Pregnancy, drug knowledge, drug side effects, teratogenic effect.

Topic: 4.4 Prenatal medicine

P171 Successful outcome in a fetus with an extremely low heart rate in a case of complete congenital heart block: a case report

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Introduction

Congenital heart block (CHB) is a rare but life threatening condition in the fetal life with an incidence of approximately 1 in 20,000 live births. The most common cause is autoimmune associated CHB which occurs in 2–5% pregnancies with positive anti Ro/SSA and La/SSB antibodies with a recurrence rate as high as 12–25% in subsequent pregnancies. Role of oral steroids, anti-inflammatory agents, beta-mimetics, IVIG and plasmapheresis for management in prenatal period is still not clear and needs further studies.

Case

We report a case of congenital complete heart block with ventricular rate as low as 37-39/ minute in a primigravida at 25 weeks of period of gestation with positive anti-Ro/La antibodies. She was started on oral Dexamethasone, salbutamol and hydroxychloroquine. Intensive fetal monitoring was done with serial echocardiography. She underwent cesarean section at 34 weeks in view of worsening of cardiac status of the fetus. Post delivery the baby required permanent cardiac pacing on postnatal day one.

Conclusion

CHB is a common cause for fetal morbidity and mortality with as high as a 9-25% risk of fetal demise and a 5-30% risk of childhood mortality. Serial echocardiography and obstetric ultrasonography from the early second trimester, timely prenatal interventions and decision of timing of delivery are crucial aspects of management. After birth, aggressive medical management should be coupled with pacing in those babies who do not respond to medical therapies alone for successful outcome.

Topic: 4.5 The placenta and the fetal membranes

P172 Interval hysterectomy for placenta percreta in patient with hemorrhagic shock in the 20th week of gestation - case study

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Context

Placenta percreta is an abnormality of placenta attachment into the wall of the uterus where it invades the wall and can go beyond it. Complications include massive hemorrhage, bladder dysfunction and severe infections during delivery. There are a numerous predisposal factors including: previous section cesarean and placenta previa. The prevalence is estimated in 1:2 pregnancies of women with placenta previa. The incidence of both placenta previa and placenta accreta is increased in patients with uterus scars and placenta previa is an increased risk for also having placenta accreta.

Objective

The aim of this study is to report of a complex case of placenta percreta managed by interval hysterectomy.

Methods

This study is a case report study of a single patient that was hospitalized in Clinical University Center of Kosovo

Patient(s)

36 years old patient in her 20-th week of gestation is admitted to the hospital as an emergency in a state of shock because of massive intrabdominal hemorrhage. She has three previous section cesarean deliveries

Intervention(s)

During laparotomy is concluded placenta percreta on the cicatrix and because of severe hemorrhage total hysterectomy was performed saving the adnexa by the main reason of patient relatively young age.

Main outcome measure(s)

The course of intervention went without complications neither lesions of close organs. The patient reanimated with 5 doses of blood and 2 doses of plasma. After 6 days of intervention the patient was released home.

Result(s)

The incidence of morbidity adherent placenta, including placenta percreta has increased significantly over the recent years due to rising of cesarean section rates. Historically abnormally invasive placenta has been managed with cesarean hysterectomy.

Conclusions

It is concluded that a correlation between previous section cesarean and abnormal placental attachment in to the uterus walls exist. Also we concluded that to save the life of the patient total hysteroscopy was surely needed.

Key words: Placenta acreta, Kosovo, section cesarean, Interval Hysterectomy.

Topic: 4.5 The placenta and the fetal membranes

P174 The features of fetoplacental angiogenesis in pregnant women with anamnestic embryonic losses

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The miscarriage is considered not only as the most important element of original selection, but also as the first manifestation of serious pathological changes, which in 30% of incidents are the cause of subsequent recurrent miscarriage. It is extremely important that 75-80% of losses were occurred within early gestational age (8-10 weeks). One of the important reasons for spontaneous miscarriage is the chorionic-placental factor, which in 40-50% of cases is the strongest predictor of the manifestation of perinatal pathology (placental dysfunction, preeclampsia, preterm birth) if pregnancy will progress. Therefore, the goal of our prospective study was to study the factors of fetoplacental angiogenesis in pregnant women with previous embryonic losses (PEL).
We were decided to investigate the role of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in the development of gestational complications in pregnant women who had previous pregnancy losses in the early gestational age.

Methods

In accordance with the task of our study, 40 pregnant women were examined, in term of pregnancy 10-12 weeks. The clinical group was represented by 20 pregnant women who had a history of embryonic losses. 20 pregnant women with a physiological pregnancy comprised a control group.

Results

According to the results of our prospective study, the difference in the serum level of VEGF between women with the physiological pregnancy (36.14 ± 3.88 pg/ml) and the clinical group (23.49 ± 2.88 pg/ml) had a statistically significant difference ($p < 0.05$). These results may indicate that placental development in pregnant women with PEL were occurred in conditions of impaired formation of processes angiogenesis and disorders local hemodynamic. An analysis of the serum data of PlGF also revealed a significant decrease ($p < 0.05$) of PlGF to 11.85 ± 2.85 pg/ml (pregnant women with PEL) against 20.17 ± 2.92 pg/ml in women with a physiological process of gestation.

Conclusion

The result of our study of endothelial angiogenesis factors in women with PEL may be evidence of impaired optimal blood flow in the uterus-placenta-fetus system and may be an early marker of placenta-dependent pregnancy complications.

Topic: 4.5 The placenta and the fetal membranes

P175 Association between prelabor rupture of membranes (PROM) and hypertensive disease of pregnancy

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Context

Prelabor rupture of membranes (PROM), previously known as premature rupture of membranes, is breakage of the amniotic sac before the onset of labor. Hypertensive disease of pregnancy, also known as maternal hypertensive disorder, is a group of high blood pressure disorders that include preeclampsia, eclampsia, gestational hypertension, and chronic hypertension

Objective

The aim of this study is to see the correlation between prelabor rupture of membranes and hypertensive disease of pregnancy.

Methods

This study is a case control study that took place in Prishtina, Kosovo. There were 107 pregnant women studied in a two year period of time. They were observed since their beginning of their pregnancy to their delivery.

Patients

In this study were studied were 107 pregnant women, their average age was 27 years old. About 57% of them lived in the city and the rest 43% in rural places. More than half of these women did not smoke during their pregnancy 73% while the rest 37% did smoke.

Main outcome measure

Some of these studied women 31.5% experienced some time of Hypertensive disease such as high blood pressure about 41%, about 24.3 % had chronic hypertension and 34.5 of all of the women that experienced hypertensive disease (about 48 women) developed gestational hypertension.

Results

Premature amniotic membrane burst (PROM), the frequency was higher in the group of pregnant women who did not show hypertensive disorders during pregnancy (13.7%) compared to the group of pregnant women who exhibited these disorders (7.4%), however the difference was not statistically significant (P> 0.05),

Conclusions

In conclusions premature amniotic membrane burst (PROM) can be correlated with Hypertensive disease but is not a very significant correlation.

Topic: 4.7 Immunological disorders and pregnancy

P178 The efficiency of Vitamin D in successful implantation

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Context

The non-classical effects of vitamin D are highly important during pregnancy: placenta contains the VDR(vitamin D-receptor) and VDR signaling pathways. Vitamin D has a role as an immune regulator during implantation. This vitamin induces decidualization, limits production of proinflammatory cytokines what can help in normalizing process of implantation in early pregnancy.

Objective

The purpose of this study is to compare the expression of vitamin D and its receptor in the villous chorionic villous among the missed abortion and induced abortion groups, investigate the level of 25(OH)D in the blood and to determine the polymorphism VDR(rs731236-TaqI) of pregnant women.

Methods

It was a prospective complex cohort study which consisted of 3 parts - clinical data, genetics and pathomorphological investigations.

Patients

The first and second parts of study included 120 pregnant women from 6-14 weeks of gestation with supervision them until delivery. The pathomorophology included 64 cases of abortion material from women with missed(n=32) and induced abortion with normal pregnancy (n=32).

Interventions

The state of vitamin D was based on the concentration of 25(OH)D, determined by enzyme immunoassay in the mother's serum. Pathomorophological investigation included H&E stain, IHC and confocal laser scanning microscopy (CLSM).

Main outcome measures and results

In 1 group was the biggest number of women with retrochorial haematoma (68,4%) among women with severe deficient of vitamin D. There were high negative correlation in group with threatening miscarriage between the level of vitamin D, homocysteine and BMI. The spreading by genotypes of this gene was not statistically different among 3 groups. Each 10th woman was the carrier of a homozygote mutation (tt). After IHC investigation the average relative area of vitamin D and VDR expression in syncytiotrophoblast were statistically lower in chorionic villous of the group with missed abortion. In complex therapy, we used cholecalciferol 2000-4000 IU per day depends on baseline level of 25(OH)D in serum and there was a positive dynamics of the increasing the level of 25(OH)D in blood (by an average of 30-40%) after 6 weeks of treatment.

Conclusion

Correction of vitamin D deficiency in pregnant women with a threatened miscarriage has been shown to be effective in treating and can be a perspective method in complex therapy of pregnancy loss.

Topic: 4.7 Immunological disorders and pregnancy

P179 Termination of a pregnancy in patient with lupus eritematosus in the 17th week of gestation due to severe complications - case study

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Context
Lupus is a long-term autoimmune disease in which the body's immune system becomes hyperactive and attacks normal, healthy tissue. Symptoms include inflammation, swelling, and damage to the joints, skin, kidneys, blood, heart, and lungs. Less than 50% of pregnancies in women with lupus have complications, but all lupus pregnancies are considered high-risk. Lupus can complicate pregnancy with an increased risk of miscarriage, premature delivery, and preeclampsia, as well as heart problems in the baby

Objective
The aim of this study is to report of a case of lupus eritematosus in pregnancy managed by discontinuation of it.

Methods
This study is a case report study of a single patient that was hospitalized in Clinical University Center of Kosovo in April 2019

Patient(s)
Patient V.K from Mitrovia, Kosovo in her 13-th week of gestation is admitted to the hospital as an emergency because of high blood pressure 160/110 mmHg.

Intervention(s)
Methyldopa 250mg 2x1 was advised to take to lower the blood pressure and further analysis were taken such as hemogram, urine and glycemia. Proteinuria was encountered and further analyses were needed. Also the patient was instructed to be examined by other doctors such as cardiologist, nephrologist, pulmonologist etc

Main outcome measure(s)
After adequate examination and tests doctors concluded that the patient has lupus eritematosus ascites with symptoms such as hypertension, proteinuria, escherichia coli vaginal infection.

Result(s)
After a consolation composed of doctors such as nephrologist, rheumatologist, cardiologist, neurologist and gynecologist in Clinical University Center of Kosovo it is concluded for a discontinuation of the pregnancy in the 17th week of gestation to preserve the mother's health. The couple also agreed to terminate the pregnancy because of its risks. After that the patient was admitted to Oncology department for further intervention in order to end the pregnancy.

Conclusions
Pregnancy in women with SLE is a high risk condition. Despite considerable improvement in success rates, substantially high maternal and fetal morbidity and mortality still remain a cause for concern. Disease activity may worsen during the pregnancy and in turn may increase the risk of other maternal and fetal complications

Key words: lupus eritematosus, pregnancy, Kosovo, hypertension

Topic: 4.8 Endocrine disorders in pregnancy

P180 Primary hyperparathyroidism recognised in pregnancy

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Hyperparathyreodism is a rare condition, and has added risk if present in pregnancy. Management requires high expertise. Primary hyperparathyroidism diagnosed in pregnany is uncommon and is most often due to a solitary parathyroid adenoma. It is usually asymptomatic, since symptoms of hypercalcemia may be difficult to diagnosis, as they are frequently similar to those of pregnancy, such as nausea, fatigue and vomiting.

Pregnant women with hyperparathyreodism has a significantly higher risk for obstetrical complications, but what is more important, the life of the fetus is in danger. The risk of early spontaneous abortion is elevated, which correlates with maternal serum calcium levels. The highest risk for fetal demise is at very high Ca-levels (above 12mg/dl), risk is up to 85% at 13 mg/dl Ca-levels. Early recognition and treatment are crucial to preventing long-term or lethal consequences. If is not recognised in time or untreated it can result in maternal preecclampsia, there might be cardiac arrythmia during labor, and preterm birth, IUGR, fetal demise is also more common. If the fetal parathyroid glands are fail to develop normally, permanent hypoparathyreodism might be present at the fetus, and postnatal hypocalcemic tetany might occur to the newborn.

We present a case of primary hyperparathyroidism due to a parathyroid adenoma in a 28-year-old G1P0 pregnant women who was diagnosed by routine laboratory result at the 7th gestational week. Urgent parathyroidectomy was required. The successful management of the patient was possible with an intensive collaboration of obstetrician, endocrinologist, surgeon, and anaesthesiologist.

Topic: 4.8 Endocrine disorders in pregnancy

P181 A case report on a rare diagnosis of pituitary apoplexy for a headache during pregnancy

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Background

Pituitary apoplexy is an endocrine emergency, which occurs from sudden infarction or haemorrhage of the pituitary gland. Symptoms include headache, vomiting, ophthalmoplegia, visual changes and altered mental state. Although pregnancy is an uncommon precipitant, the severe neurologic and endocrine consequences underline the importance of this potentially fatal diagnosis in the pregnant patient who presents with a headache.

Case

A 27-year-old woman G4P2, 27+4 weeks-gestation presented to the emergency department with sudden onset headache, associated with nausea and vomiting. She was on low dose aspirin for pre-eclampsia prophylaxis, in the context of a low PAPP-A identified during her first trimester screen. The patient's obstetric history was remarkable for gestational insulin dependent diabetes in two of her previous pregnancies, both delivered by caesarean section. There was no significant medical, surgical or family history. On admission, neurological examination was unremarkable. A Magnetic Resonance Imaging (MRI) study demonstrated a hyperintense T1 signal in the posterior adenohypohysis, concerning of a recent pituitary gland haemorrhage and apoplexy. There was no evidence suggesting compression of the optic chiasm or cranial nerves, and no venous sinus thrombosis. A pituitary panel showed normal pituitary hormone levels, with cortisol (1464 IU) and prolactin (800 IU) within the expected limits of pregnancy. She did not require any hormone replacement therapy and her low-dose aspirin was ceased, understanding the potential risk of pre-eclampsia. The patient's antenatal course was otherwise uneventful, managed in the outpatient setting through the high risk obstetric and endocrine clinic. She was delivered by caesarean section and underwent repeat MRI 6 weeks post-partum to exclude an underlying pituitary adenoma.

Discussion

Pituitary apoplexy is rare in pregnancy, and in the absence of previous pituitary tumours, is thought to be caused by physiological oestrogen-stimulated lactotroph hyperplasia of the pituitary gland. Without worsening neuro-ophthalmic signs, pituitary apoplexy can be managed conservatively in the acute stage. However, trans-sphenoidal surgery is indicated if there are signs of neurological or ophthalmic compromise. Patients need close surveillance of pituitary bloods and urgent replacement of the deficient hormones. Follow up post-partum is critical for diagnosis of any underlying pituitary tumours.

Topic: 4.8 Endocrine disorders in pregnancy

P182 The effectiveness of cholecalciferol in the treatment of postpartum osteopenia

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Introduction

According to the literature, the prevalence of vitamin D deficiency and deficiency in pregnant women reaches 60-80%, which is a significant factor in reducing BMD, the development of osteopenia, and the risk of fractures after childbirth.

Aim

To assess the factors affecting the recovery of BMD after childbirth with 400 IU of colecalciferol.

Materials and methods

124 puerperas were included in the study. On day 3-5 all the women in labor were screened for the distal and axial parts of the skeleton using X-ray absorption densitometry. According to the results all women included in the study are divided into 2 groups: The main group: puerperas with BMD corresponding to osteopenia (n = 65 women); The comparison group consisted of puerperas with normal BMD(n = 52 people). All women are prescribed vitamin D 400 IU for 6 months after childbirth. Serum levels of 25-hydroxycalciferol, calcium, prolactin, osteocalcin, β-isomer of type I collagen C-terminal telopeptide were determined by immunoassay.

Results

Analysis of the distribution of BMD with osteopenia and with normal BMD had a similar trend. In the group with osteopenia, the lowest BMD in the lumbar region at the level of L1 (1,006 ± 0.12 g / cm^2), in the proximal femur in the greater trochanter(-0.746± 0.09 g/cm^2), the lowest BMD in the forearm – in the ultradistal forearm (0.34±0.03 g/cm^2).6 months after birth, there was a decrease in BMD in the trochanter and ward area, proximal femur (-0.726= 0.09 g / cm^2) reduction of BMD at L1 level in lumbar spine, decrease in BMD in the distal forearm. The dynamics of BMD after 6 months in the distal forearm, proximal thigh and spine depended on the initial level of vitamin D (r= 0.68) and osteocalcin (r=0.35). A negative increase in BMD after delivery in the lumbar spine is associated with crosslab levels, pregnancies less than 2 years apart, and overweight. The dynamics of BMD in the distal forearm and lumbar spine at 6 months (r= 0.71) and 12 months depended on the presence of preeclampsia during pregnancy (r= 0.52). Prolactin gain is associated with a smaller increase in BMD in the proximal femur lumbar spine (r= -0.48). The increase in vitamin D is associated with an increase in BMD in the distal forearm.

Conclusions

Preeclampsia, baseline vitamin D levels, overweight-factors that affect the recovery of IPC after childbirth. In the postpartum period, lactation is a factor of delayed bone tissue recovery

Topic: 4.9 Neurodegenerative disorders in pregnancy

P182b Neurofibromatosis morbus Recklinghausen in pregnancy - case report from Kosovo

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Context

Neurofibromatosis type I is a complex multi-system human disorder caused by the mutation of a gene on chromosome 17 that is responsible for production of a protein called neurofibromin-needed for normal function in many human cell types. Although numerous studies suggest an increased incidence of pregnancy complications in patients with NF1, relatively fewer reports describe the effect of pregnancy on cutaneous manifestations of NF1.

Objective

The aim of this study was to see if NMR in pregnancy affected the cesarean cut of the abdominal, anesthesia for the delivery and the recuperation of the patient.

Methods

This study is a case report study of a single patient that was hospitalized in Clinical University Center of Kosovo in September 2019 and delivered her baby at 36 weeks of gestation by section cesarean. She had a previous SC for her firstborn because of fetal disproportion.

Patient

N.B age 32 mother of a three year old, has been diagnosed at the age of 13 with NMR after she noticed some different pigments and lesions on her skin located mostly on her abdomen. The patient denied any other complications during her pregnancy and had regular follow-up with her obstetrician throughout her pregnancy. The patient admitted that her uncle was previously diagnosed with NMR Intervention After a consolation of the doctors in Clinical University Center of Kosovo it was decided that the delivery should be by SC, also the patient required to deliver her baby by SC.

Main outcome measure

The delivery was performed at 36 weeks of gestation and according to her latest ultrasound visit the fetus was in a slight IUGR and with the perception of oligohydramnios. The anesthesiologist started to administrate anesthesia and the patient reacted to it with difficulties then the obstetrician performed the abdominal cut and after several minutes the fetus was delivered. Its weight was about 2000 gram with an Apgar Score of 6/7. The fetus had slight IUGR and was sent to incubator for 7 days. After its release the baby was completely healthy.

Results

The patient after her hospitalization due to her delivery didn't show any further complication and was sent home along with her baby. She came to visit after 10 days and her surgical wound was showing signs of full recovery.

Conclusions

We consider that this study will be beneficial to doctors so they can complement their professional experience with more extensive knowledge on differential diagnosis and clinical manifestation.

Topic: 4.11 Obesity and fetal and maternal risks

P183 Influence of over weight on pregnancy and its outcome

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Context

Overweight is currently a socially significant issue that is epidemic-wide. 39% of people worldwide are overweight, in Ukraine this figure is 58%. Pregnancy is one of the trigger factors for the development of obesity, since the most favorable conditions are created for the development of fatty tissue, which serves to protect the baby in the womb. During pregnancy, significant hormonal changes occur in the mother's body, which also stimulates the deposition of adipose tissue in the woman's body.

Objective

To determine the effect of overweight on pregnancy and its outcome.

Methods

An analysis of the course of pregnancy and childbirth in 76 women was carried out at the Department of Obstetrics, Gynecology and Pediatric Gynecology of KhNMU. Pregnant women were divided into 2 clinical groups: group I (main) - 46 overweight women, group II (control) - 30 women with normal body weight. The average age of the patients is 30.5 years (from 19 to 42 years). Outpatient cards, exchange cards of pregnant women, history of childbirth and newborns are analyzed.

Results

It was found that 86.9% (40 women) with overweight had extragenital pathology, in the control group this indicator was 20% (6 women). Patients of group I observed: arterial hypertension in 60.9% (28 women), vegetative-vascular dystonia in 80.4% (37 women), autoimmune thyroiditis in 56.5% (26 women), chronic gastritis in 43.5 % (20 women) and pyelonephritis in 60.9% (28 women). In addition, varicose veins of the lower extremities were observed in 80.4% (37 women) of the main group. In 82.6% (38 women) of group I, pregnancy was complicated: preeclampsia of the first half of pregnancy (60.9%), threatened abortion (39.1%), preeclampsia of varying severity (82.6%), whereas in group II group toxicosis of the first half of pregnancy was observed in 26.6% (8 women), the threat of termination of pregnancy - in 13.3% (4 women). The threat of preterm birth in 26% (12 women) of the 1st group and 6.6% (2 women) of the 2nd group. There was no significant difference in delivery time and duration of labor. In group I, 65.2% (30 women) were delivered by cesarean section, 34.8% (16 women) gave birth through the natural birth canal; in group II - 16.6% (5 women) and 83.3% (25 women), respectively. The course of the postpartum period and birth weight did not differ significantly.

Conclusions

Overweight of women negatively affects the course of pregnancy and its outcome.

Topic: 4.11 Obesity and fetal and maternal risks

P184 Early pregnancy excess weight and gestational diabetes in Latvian pregnant women

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Context
High body mass index (BMI) during pregnancy is a risk factor for several pregnancy complications, including gestational diabetes (GD), and also has short and long term adverse effects on neonate health. The prevalence of women with excess weight in Latvia is increasing – almost 60% of women are overweight or obese. Healthcare professionals have their role in weight reduction and nutrition counselling, therby adding to complication rate reduction of excess weight (EW) and GD.

Objective
The goal was to investigate EW prevalence in Latvian pregnant women, its association with GD, and nutritional counselling provision.

Methods
A cross-sectional survey took place in maternity outpatient clinics in Latvia from August 2017 until November 2019. Data was obtained from medical records and a pregnancy dietary and lifestyle habit questionnaire. Data was processed with IBM SPSS statistics.

Patients
Inclusion criteria: women until seventh day after delivery, pregnancy counselling initiated prior to 12 weeks of gestation, singleton pregnancy.

Main outcome measures
BMI categories: underweight < 18.5 kg/m^2; normal weight: 18.5 - 24.9 kg/m^2; overweight 25 - 29.9 kg/m^2; obesity ≥ 30 kg/m^2. GD was diagnosed according to IAGDP, when any of the following three 75 gram 2-hour oral glucose tolerance test (OGTT) thresholds were met or exceeded: fasting 5.1 mmol/L, one hour 10.00 mmol/L, two hours 8.3 mmol/L.

Results
In total, 533 women were included. Based on early pregnancy BMI, 4% were underweight, 64% had normal BMI, 22% were overweight, and 9% were obese. Overall, 33% of pregnant women had EW. Of these, 61% were screened for GD. GD was diagnosed in 37% of EW group women. The majority, or 69% of EW group had never before pregnancy received advice to reduce weight; the minority received advice from medical professionals (11%) or family members (9%). Nutritional counselling during pregnancy due to health issues was received mostly from obstetricians (64%), other health professionals (25%), and family members (11%). The most popular sources of information on nutrition recommendations during pregnancy were Internet and social media (36.6%), health professionals (26%), family and friends (15%), and specialized books (12%).

Conclusions
The prevalence of EW in early pregnancy is high. The GD screening in Latvia should be improved for risk groups. Adequate nutritional counselling for women with EW, especially in pregnancy planning period, should be provided.

Topic: 4.12 Pregnancy and lifestyle

P185 Role of diet and lifestyle in obese pregnant women - case series

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Context
Obesity is an increasingly pathology common in young patients. Few patients are compliant with diet.

Objective
We wanted to see if obese patients with a BMI over 30kg / m^2 with a weight gain of 5-8 kg or less in pregnancy have good outcomes. We also analyzed the diet and the lifestyle changes needed to obtain these objective.

Methods
We followed a number of 9 obese patients who followed a strict diet in pregnancy compared to 9 obese patients who neither followed the diet, nor had lifestyle changes. The diet consisted of 4 meals a day at 3-4 hours, being normoproteic, normolypidic and hypoglucidic, without processed sugars.

Results and Conclusions
We observed good results regarding weight gain, glycemic control and pregnancy outcome in patients in the diet group. These patients had a total weight gain of less than 6 kg in pregnancy. Patients who did not change their diet and lifestyle had worse maternal-fetal outcomes with a weight gain over 15 kg. In conclusion, a balanced pregnancy diet in obese patients can improve pregnancy progression without affecting the newborn, while patients who do not follow a controlled diet by either diabetes or gynecologist are at increased risk of developing gestational diabetes and hypertension and have macrosome fetuses and polyhydramnios.

Topic: 4.12 Pregnancy and lifestyle

P186 Relationship between the consumption of carbohydrates and minerals in pregnant Mexican patients

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Context

It is well established that good maternal nutrition is a key factor in preventing obstetric complications, infant morbidity and mortality. During pregnancy, it is important to consume the recommended daily intake (RDI) of carbohydrates and minerals.

Objective

Analyze the relationship between energy intake of carbohydrates and minerals of pregnant Mexican patients.

Material y methods

descriptive and observational study of 140 records of pregnancy women aged 14 to 40 years. Variables collected anthropometric data and clinical characteristics. To analyzed energy intake we applied 24-hour recall. We classified the adequacy consumption into four categories, deficient (> 67%), good (68-69%), adequate (90-110%) and excess (<110%). Descriptive and inferential statistics applied. Chi squared and Pearson correlations were applied.

Results

Mean age of patients was 22, 45 ± 5, 6 years, mean initial gestational week was 15, 05 ± 4, 4 weeks. Mean height was 1.56 ± 0.06 meters, mean gestational weight 62, 05 ± 13.3kg, mean gestational BMI was 25.6 ± 5,2kg / m^2. Deficient and excessive intake (24.3%) was observed equally on the total energy intake. Carbohydrate intake was excessive 30.7% (n=43). Significant differences were observed between deficient carbohydrate and sodium intake (57.1%) (n=20) and excess carbohydrate and sodium intake (55.8%) (n = 24) (p =0.003). Also excess consumption of carbohydrates, selenium and phosphorus are related (p=0,000; p = 0.006). Another significant differences were observed between deficient carbohydrate, potassium, magnesium, iron and calcium intake (p=0.018; p=0,000; p =0.001; p = 0.033).

Conclusions

Compared with the daily recommendations intake in pregnancy, our results show an inadequate consumption, so a nutritional intervention during pregnancy is necessary. Nutrition plays a fundamental role in the development of a healthy child.

Topic: 4.12 Pregnancy and lifestyle

P187 Changes of steroid hormones in pregnant ex-smokers and their newborns

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Context

Smoking has many effects on human health and reproduction. Women are generally recommended to quit smoking before conception. Cessation improves fertility and helps avoid many health risks for the mother and the child.

Objective

We performed a study following changes in the production of steroid hormones in pregnant smokers and ex-smokers compared to non-smokers. In physiological pregnancies, there are differences in the levels of steroid hormones in a pregnant woman depending on the sex of the fetus, and there are differences in the steroids of newborns depending on their sex and the type of delivery.

Methods

We have focused on changes in steroidogenesis in the blood of mothers in their 37th week of pregnancy and in mixed cord blood of their newborns. The study included 47 healthy women, of which 14 were active smokers, 11 ex-smokers (smoking cessation lasts more than a year), and 22 non-smokers. All women had physiological course of gravidity, gave birth spontaneously, and carried female fetus. Selected steroid hormones (cortisol, cortisone, dehydroepiandrosterone, 7α-hydroxy-dehydroepiandrosterone, 7β-hydroxy-dehydroepiandrosterone, 7-oxo-dehydroepiandrosterone, pregnenolone, 17α-hydroxy-pregnenolone, testosterone, androstenedione, progesterone, 17-OHprogesterone, corticosterone, estrone, estradiol, and estriol) were measured using methods LC-MS/MS. Local ethical committee approved the study.

Results

We found higher levels of androstenedione and lower levels of 17-OH-pregnenolone at the 37th week of pregnancy in smokers and ex-smokers compared to non-smokers. The levels of 7β-OH-DHEA, 7-oxo-DHEA were lower in smokers compared to ex-smokers and non-smokers. Other measured steroids did not differ for ex-smokers or smokers.

We have measured lower levels of 7α -OH-DHEA in female newborns delivered by non-smokers compared to other groups, while other measured hormones showed no significant differences.

Main outcome measure

Even a history of smoking can induce changes in the production of steroids during pregnancy.

Conclusions

Our study shows that hormonal dysbalances found in pregnant ex-smokers could be similar to pregnant smokers for some steroids, while levels of other steroids will normalize with abstinence. This finding correlates with our data from previous studies and studies of other authors about long lasting influence of smoking on steroid metabolism.

Topic: 4.12 Pregnancy and lifestyle

P188 Relationship between carbohydrates and vitamins intake of pregnant mexican patients

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Context

Nutritional status is decisive in pregnant woman, especially in new born. Low amounts of macronutrients and vitamins affects birth weight, decreases oxidative stress during the delivery and recovery of the new born.

Objective

Analyze the relationship between energy intake of carbohydrates and vitamins of pregnant Mexican patients.

Material y methods

Descriptive and observational study of 140 records of pregnancy women aged 14 to 40 years. Anthropometric data and clinical characteristics were collected. The 24-hour reminder evaluated food consumptions. Percentage (%) of adequacy was determined as follow: deficient (> 67%), good (68-69%), adequate (90-110%) and excess (<110%). Descriptive and inferential statistics applied. Chi squared and Pearson correlation contrast data between variables.

Results

Mean age of patients was 22, 45 ± 5, 6 years, mean initial gestational week was 15, 05 ± 4, 4 weeks. Mean height was 1.56 ± 0.06 meters, mean gestational weight 62, 05 ± 13.3kg, mean gestational BMI was 25.6 ± 5,2kg / m^2. In the percentage of adequacy in energy, they had both deficient and excessive intake (24.3%). In the percentage of adequacy in carbohydrate intake, 30.7% (n=43) excess intake. Significant differences were found between carbohydrate intake and excess vitamin D intake (74.3%) (n = 104) (p = 0.048), significant differences between carbohydrate intake and deficient vitamin B6 intake (55.7%) (n=74) (p= 0,000), significant differences between carbohydrate intake and deficient vitamin B3 intake (12.9%) (n = 35) (0.015), significant differences between carbohydrate consumption and excess vitamin B2 consumption (17.1%) (n = 40) (0.000) and significant differences between carbohydrate consumption and excess vitamin B1 consumption (13.1%) (n = 34) (0,000).

Conclusions

These deficiencies in diet can produce harmful effects on the mother and the product, it is recommended a nutritional intervention since the first prenatal visit, so that we can avoid the appearance of this deficiency.

Topic: 4.12 Pregnancy and lifestyle

P189 Nitrous oxide vs epidural analgesia during labor

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Context

The pain from labor and delivery has distinct levels of perception from a person to another and it can be also different from one labor to another for the same person. The sense of pain depends on the emotional, social, cognitive, cultural and motivational circumstances of every single person. Reducing the labor pain represents an important target for every health system in the developed countries. From distinct types of analgesia, the epidural and the nitrous oxide analgesia have an elevated level of efficiency, compliance and availability.

Materials and methods

We present the experience of Polizu Department from Alessandrescu - Rusescu" National Institute for Mother and Child Health, on epidural and nitrous oxide analgesia during labor and delivery. The patients were separated in 2 groups: one that received nitrous oxide and the other that received epidural analgesia. The main parameter evaluated via questionnaires, was the pain perception before and after analgesia. The surveys were elaborated in the first 2-3 days after delivery. Other questions were about the self-confidence regarding the self- administration of nitrous oxide and the confidence in the doctor for epidural administration. The clinical examination was used to note the side effects of the both methods, the total duration of the administration, the mode of delivery and the Apgar score.

Results

The epidural analgesia has indisputable advantages in reducing the pain intensity. On the other side, it has some disadvantages. It is an invasive method for analgesia with different complications that may require the presence of the anesthesiologist. Because of its intense effect of reducing the pain perception, a long time it was preferred over other types of analgesia. Although the efficiency, complications, contraindications and side effects of nitrous oxide analgesia can be comparable with the epidural ones, it is not preferred among patients and the reason for this can be the lack of knowledge of the advantages of the treatment with nitrous oxide.

Conclusions

Both epidural and nitrous oxide analgesia can be used in reducing the pain during labor and delivery. They both have multiple benefits for the mother and as well the child.

Topic: 4.13 Preterm labor and delivery

P191 Maternal blood and amnionic oxytocin receptor gene expression and serum oxytocin levels in preterm birth: a case control study

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Context

Preterm birth (PTB) is a major determinant of neonatal mortality and morbidity and has long term adverse consequences for health. Until recently very few studies are available which explore PTB at the gene expression level. The oxytocin (OXT)-oxytocin receptor (OXTR) system provides promising candidate gene for studies of genetic contributions to prematurity in the diagnosis, prevention and treatment of PTB. Research at the gene expression level of OXTR can lead to a better understanding of the mechanisms of initiating labour in general and thus should make it possible not only to treat preterm birth effectively, but to find out better ways of inducing preterm births in pathological pregnancies requiring early termination.

Objective

Quantification and comparison of oxytocin receptor (OXTR) gene expression and serum OXT levels in the blood and amnion of women delivering preterm with term controls. Evaluation of the correlation between OXTR gene expression in blood and amnion with serum oxytocin levels in women delivering preterm.

Methods

70 pregnant women delivering preterm i.e < 37 weeks and equal number of matched controls delivering spontaneously at term (37-42 weeks) were recruited. Maternal serum OXT levels in active stage of labor i.e 4 cm cervical dilatation were quantified by ELISA (Enzyme Linked Immunosorbent Assay). Gene expression studies in the maternal blood and amnion were done by using real time quantitative polymerase chain reaction (RT-qPCR).

Main outcome measure

OXTR gene expression in maternal blood and amnion of PTB cases and correlation between OXTR gene expression in blood and amnion with the serum OXT levels in women delivering prematurely.

Results

The mean serum OXT level in PTL was 48.56 ± 6.97 pg/ml; significantly higher than in controls (43.00 ± 3.96 pg/ml), $p<0.001$. OXTR gene expression both in maternal blood (2.5 times) and amnion (3.5 times) were significantly higher in PTL. A significant positive correlation was observed between serum OXT levels and OXTR gene expression in amnion ($r = -0.190$, $p = 0.025$).

Conclusions

The serum OXT levels surge significantly in active phase of PTL. There is much higher rise in OXTR gene expression in amnion. Thus, amnion as a major site of prostaglandins (PTGs) production probably links OXT-PTGs autocrine paracrine circuit to facilitate PTL. Future studies are needed to devise better OXTR receptor antagonists preferably acting on amnionic OXTRs to prevent PTL.

Topic: 4.13 Preterm labor and delivery

P192 Genetic polymorphisms in the MMP9 and TGFß1 genes in women with cervical insufficiency

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Objective

Premature shortening of the cervix and cervical insufficiency (CI) may be induced by constitutional weakness of the cervix against the background of genetically determined abnormal connective tissue metabolism. The aim of this study was to assess the association between cervical insufficiency and single nucleotide polymorphisms (SNP) in matrix metallopeptidase 9 (MMP9) and transforming growth factor β1 (TGFβ1) genes, encoding connective tissue metabolism.

Methods

In a case-control study medical, obstetric histories and blood were obtained from singleton pregnant women at 22–24 gestational weeks with (n=36) and those without (n=35) cervical insufficiency. DNA was extracted by using commercial DNA isolation kits. Serum levels of MMP9 and TGFβ1 was determined by enzyme immunoassay (ELISA). Genotyping was carried out in SNPs A-8202G MMP9 gene (rs11697325) and Arg25Pro TGFβ1 gene (rs1800471) by using an allele-specific polymerase chain reaction assay.

Results

Women with cervical insufficiency had higher serum concentrations compared with controls of both MMP9 (1.4 ± 0.3 ng/ml; mean ± SD versus 1.0 ± 0.3 ng/ml; p = 0.000002) and TGFβ1 (32.2 ± 12.0 ng/ml vs 16.4 ± 5.7 ng/ml; p = 0.0001).

Also, we found a negative correlation between serum MMP9 level (but not for TGFβ1) and cervical length in women with cervical insufficiency (r = -0.49, p = 0.0025).

Two genotypes were significantly associated with cervical insufficiency compared with controls: homozygous carriers of the MMP9 –8202G allele (genotype G/G) (odds ratio (OR) 4.0; 95% confidence interval (95% CI) 1.23–12.98; p = 0.02) and carriers of the Arg/Pro genotype TGFβ1 gene (OR 3.75; 95% CI 1.88–7.47; p = 0.0001).

Carriers of GG genotype of the MMP9 gene had significantly higher serum MMP9 concentration than homozygotes by allele A–8202 (AA) and heterozygotes (AG) (1.7 ± 0.2 ng/ml vs 1.3 ± 0.2 ng/ml; p = 0.0017 and 1.4 ± 0.4 ng/ml; p = 0.007 respectively).

These observations suggest possible links in the pathogenesis of cervical insufficiency: the presence of a mutant genotype of the MMP9 gene → increased production of MMP9 → activation of collagenolysis connective tissue structures of the cervix → shortening and softening of the cervix during pregnancy.

Conclusions

GG genotype of the A-8202G polymorphism MMP9 gene and ArgPro genotype of the Arg25Pro polymorphism TGFβ1 gene are associated with a high risk of cervical insufficiency.

Topic: 4.13 Preterm labor and delivery

P193 Comparison of oral misoprostol with intramuscular oxytocin in the active management of third stage of labour

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Objective
This study aimed at comparing the efficacy of oral misoprostol 600 mcg with intramuscular oxytocin 10 IU in the active management of third stage of labour.

Methods
This prospective comparative study was performed in Tribhuvan University Teaching Hospital, Kathmandu, Nepal to compare the efficacy of oral misoprostol with intramuscular oxytocin in the third stage of labour for the prevention of postpartum hemorrhage(PPH).

Patients
One hundred and twenty women without risk of PPH were randomly allocated to receive either 600 mcg misoprostol orally (Group A) or 10 unit of oxytocin intramuscularly (Group B) within 1 minute of delivery.
Interventions and Measures: The efficacy and the safety of these two drugs were analyzed on the basis of percentages fall in hemoglobin (Hb) and hematocrit (Hct) level from before delivery to 8 completed hours after delivery, need for additional uterotonic agents, need for exploration and uterine evacuation, need for blood transfusion, duration of third stage of labour and the numbers of retained placenta and need for MRP.

Results
Oral misoprostol was observed to be equally effective as intramuscular oxytocin in prevention of post-partum hemorrhage (PPH). There was no statistical difference in the duration of third stage of labour, need for additional uterotonics, need for uterine exploration/evacuation and need for blood transfusion in the two groups.

Conclusions
Routine use of oral misoprostol 600 mcg appears to be as effective as 10 IU intramuscular oxytocin in minimizing blood loss during the third stage of labour.

Keywords: active management of third stage of labour; misoprostol; oxytocin.

Topic: 4.13 Preterm labor and delivery

P193b Determining preterm labour through fetal fibronectin and phosphorylated insulin-like growth factor binding protein-1 tests - which to choose?

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Objective

The main problem for fetal morbidity and mortality in XXI century is still the prematurity. It is very highly searched how to predict women who will give preterm labour. The most widely used method of ultrasound examination of the cervical length can determine the patients at highest risks, but there is no stable cutoff for the length. Therefor were found clinical biomarker tests in the cervico-vaginal fluid for predicting preterm labour - two of them are the fetal fibronectin (fFN) and phosphorylated insulin-like growth factor binding protein-1 (phIGFBP1). The aim of the study was to compare the predictive values from measuring the cervical length plus one of the followings: the fFN or the pIGFBP-1.

Methods

A prospective, cross-sectional study was designed, dividing patients in 2 groups: Group A - with clinical symptoms of preterm birth and Group B - patients with no symptoms of preterm. All patients that were included in the study had a test of fFN or pIGFBP-1 performed, followed by a transvaginal measurement of the cervical length. The results from the test of fFN and pIGFBP-1 were blinded, all of them received same management and care, respectably. The pregnancy outcome was collected to be analyzed.

Results

Comparing the results between fFN and pIGFBP-1 shows very similar characteristics. All patients from group A that were positive on either fFN and pIGFBP-1 and had shortening of the cervix less than 25 mm, delivered in 2 weeks no matter the strong tocolytic therapy. The results from Group B show false positive predictable value of both tests when there are no clinical symptoms and no shortening of the cervix. Both tests showed high predictive value when negative result.

Conclusions

The modern obstetrics cannot afford to skip the problem of the premature. Even so, the currently used methods for prediction are showing unsatisfactory predictive efficacy if used one by only. What we really need is to either find new methods for screening for preterm birth and/ or improve the ones we are already using. The perfect management steps for predicting preterm labour are still unknown, despite there is more to be researched. Probably, the efforts should be directed how to determine the women about to deliver preterm and to postpone the labour as long needed to be transferred to a unit capable to provide effective preterm neonatal care while in the same time use corticosteroids for stimulating lung maturation.

Topic: 4.13 Preterm labor and delivery

P194 The effective strategy of prevention preterm birth with women with a previous history of PB

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Prediction and prevention of premature birth (PB) are an important area of modern obstetrics. The main requirements for preventive measures should be their timeliness (up to 22 weeks of pregnancy) and effectiveness. The high-risk group for PB includes pregnant women with impaired obturation cervical function. Cervical incompetence (CI) is the insufficiency of the circular musculature of the internal os, which contributes to the development of insolvency of the obstructive function of the cervix. CI was found in every 3-rd case of preterm birth. The use of cervical cerclage pessary (CCP) from 14 weeks of pregnancy, even with multiple pregnancies, is a modern method for effective prevention strategy of PB.

The aim of the study was to determine the effectiveness of CCP in pregnant women with a previous history of PB.

64 women with a singleton pregnancy with the previous history of PB were included in our prospective investigation. Pregnant patients were randomly assigned to the installation of a CCP in 14-16 weeks of gestation (n = 34) or preventive management with vaginal progestin from 20 weeks (n = 30). As clinical outcomes, we assessed the amount of PB (up to 28 weeks, up to 34 weeks, up to 37 weeks), cases of preterm rupture of membrane, cases of vaginal dysbiosis, and cases of labor dystocia.

We delineated the clinical effectiveness of CCPs in reducing the incidence of PB to 28 weeks 0% versus 6,7% for progestin therapy respectively; to 34 weeks RR 0,44; 95% CI 0,09 to 2,24, P=0,32 and cases of preterm rupture of membranes (RR 0,71; 95% CI 0,21 to 2,39, P=0,58). There were 5 and 8 cases of labor dystocia (RR 0,55; 95% CI 0,20 to 1,50, P=0,24), respectively. 70,6% of pregnant women with CCPs there were vaginal dysbiosis versus 66,7% who used vaginal progestin (RR 1,06; 95% CI 0,76 to 1,48, P=0,74).

The CCP, as well as a vaginal progestin, had effective prevention of preterm birth in singleton pregnancy among women with the previous history of PB. The differences between the selected strategies were not significant.

Topic: 4.13 Preterm labor and delivery

P195 Uterine fibroids and the risk of preterm birth: a meta-analysis

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Background

Uterine fibroids (UFs) have been related to negative obstetric outcomes, although the evidence of their effect on preterm birth risk is controversial.

Design

We searched in 5 datafiles for scientific publications reporting the risk of preterm birth (PB) in women with and without UFs as studied by ultrasound exams. The primary outcome was PB risk (delivery < 37 weeks). Effects were reported as risk ratios (RRs) and their 95% confidence intervals (CIs). Random-effects models and inverse variance method were used to meta-analyze associations between the presence of UFs and the risk of PB. Quality of the included studies was assessed with the Newcastle-Ottawa scale.

Results

Women with UFs presented a higher risk of PB < 37 weeks (RR = 1.43, 95% CI 1.27-1.60, P < 0.001) and also < 34 weeks (RR = 1.79, 95% CI 1.32-2.42, P < 0.001). Both associations (< 37 and < 34 weeks) had moderate degrees of heterogeneity. In addition, women with UFs were at higher risk of threatened preterm labor, preterm premature rupture of membranes, fetal malpresentations, placental abruptions, lower gestational age and birthweight at delivery and a higher cesarean delivery rate.

Conclusion

Pregnant women with UFs are at increased risk of PB and several obstetrical adverse outcomes.

Topic: 4.13 Preterm labor and delivery

P196 Baseline analysis from retrospects on AMH profile on challenged parenthood for exploratory prospective study

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Retrospective baseline study for exploratory prospective planning on Probability of conception among challenged parenthood

Context

This retrospective baseline analysis was observational study focussed on cross sectional population awaiting conception among challenged parenthood.

Objectives

1) Probability of conception and waiting time among challenged parenthood.
2) Identifying the profile of diagnostic variables and its associations among various categories of patients.

Usefulness of the study

-Patient's waiting time to conceive
-Doctors knowledge for timely intervention
-It answers which variable decides the probability of conception and its variation over period.

Methods

The history of patients were taken for 20 couples at random order to determine the above objectives
Intervention:
To determine the timing of intervention for IVF or ICUI and combination

Main measurable measures

Probability of conception, for it's specific cases of PCOS, nil reports and ODD's(other disorder dysfunctions)

Results

Cost and duration of treatment is reduced by early detection through AFC and AMH observations.
Waiting time increases by 7 times in the case of PCOS as compared to negative reported cases of PCOS
AFC could be used for predicting the probability of conception over a period of time.

Conclusion

AFC must be checked on challenged parenthood.
AFC on an average 1 count almost reduces every year and AMH reduces 0.27 ng/ml.
What combination of intervention at what time due to what combinational variables are decided by prescriptive analytics from prospect data with a separate frame work for PCOS

Topic: 4.14 Gestational hypertension, pre-eclampsia and eclampsia

P197 Analysis of copy number variation of the PSG11 polymorphism in pregnant women complicated with preeclampsia

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Background

Current research is focused on analyzing the contribution of inheritance in the development of preeclampsia (PE). For this reason, the study of a specific polymorphism associated with PE takes an important role. Pregnancy Specific β1 glycoprotein (PSG), is one of the oncofetal proteins produced during pregnancy and in malignant trophoblastic tumors. During normal pregnancy, PSG levels correlate positively with the term of pregnancy and represents a biochemical marker that assesses the formation and functioning of fetal-placental unit.

Objective

To analyze copy number variation (CNV) of the PSG11 polymorphism in pregnant women complicated with PE.

Methodology

Genomic DNA was extracted from cryopreserved whole blood of 125 nulliparous gestations complicated with PE and 128 healthy controls. A 593 bp fragment of the PSG11 polymorphism was amplified using PCR technique. The amplification reaction was carried out in a final volume of 25 µl, with 2 x Gotaq Master mix, 7 µM of specific primer and ultrapure water. The amplified and digested product of the samples was separated by electrophoresis in 1000% agarose gel, stained with sybersafe and visualized under UV illumination from where a photographic record was obtained.

Results

Of the total of studied samples (n = 253) a CNV of the PSG11 polymorphism was observed in 3 cases and in 2 controls (OR: 1.54, 95% CI: 0.25-9.43, p=0.488). It was also observed that the cuts presented were different from the universal fragments in our study population.

Conclusion

Although there was a trend for more CNV of the PSG-11 polymorphism among cases; this difference was not significant as compared to controls. The Sequencing of this CNV is required as they differ from universal fragments

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P198 Biochemical markers related to the prediction of preeclampsia and their association with the C677T polymorphism of the methylenetetrahydrofolate reductase gene in fetal circulation

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Background

Several biochemical markers have been related to the prediction of preeclampsia (PE). Despite this, current research indicates that the genome plays an important role in the altered secretion of these markers.

Objective

To correlate the levels of various PE predictive biochemical markers with the presence of genetic variants of the C677T polymorphism of the methylenetetrahydrofolate reductase gene in fetal circulation in women complicated with PE.

Methodology

This was a case-control study in which cryopreserved blood samples from umbilical cord (artery and vein) of women complicated with severe PE were analyzed (40 cases: artery, n = 20 and vein = 20) and their respective 40 controls (artery, n = 20 and vein, n = 20) to measure placental growth factor (PlGF), pregnancy-associated plasma protein A (PAPP-A), free β-HCG and homocysteine. In addition, DNA was extracted and then the C677T polymorphism was amplified using FRLP-PCR. Analyte levels were correlated to genetic variants.

Results

Lower PlGF and higher PAPP-A and free β-HCG levels (in vein and umbilical artery) were found in PE cases as compared to controls. NO differences were observed for homocysteine among studied groups. There was a non-significant trend in the umbilical vein for lower PIGF and higher PAPP-A and β-free HCG levels according to the genetic variants of the C677T polymorphism.

Conclusion

Biochemical markers levels showed differences in relation to the genetic variants of the C677T polymorphism; although these were not significant, possibly due to the sample size. More research is warranted in this regard.

Topic: 4.14 Gestational hypertension, pre-eclampsia and eclampsia

P199 The association between interpregnancy interval and adverse pregnancy outcomes in the United States

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Objective
Prior studies have demonstrated that short and long interpregnancy intervals are associated with increased risks of various adverse pregnancy outcomes. The objective of this study was to determine the association between interpregnancy intervals and understudied adverse pregnancy outcomes.

Methods
Birth certificate data, representing 100% of all births that occurred in the United States in 2018, were used. This analysis was limited to women who had complete information on the exposure, outcomes, and other key variables (n=2,114,546). Interpregnancy interval was defined as ≤18 months (i.e. short), 19-35 months (i.e. intermediate), and ≥36 months (i.e. long). Adverse pregnancy outcomes included gestational diabetes, gestational hypertension (including pregnancy-induced hypertension and preeclampsia), and eclampsia. Multivariate logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results
In the unadjusted models, women with short interpregnancy intervals had decreased odds of all the adverse pregnancy outcomes as compared to women with intermediate interpregnancy intervals (eclampsia: OR=0.97, 95% CI: 0.89, 1.06; gestational diabetes: OR=0.88, 95% CI: 0.87, 0.90; and gestational hypertension: OR=0.95, 95% CI: 0.93, 0.97). In contrast, women with long interpregnancy intervals had statistically significant increased odds of the adverse pregnancy outcomes (eclampsia: OR=1.50, 95% CI: 1.39, 1.62; gestational diabetes: OR=1.43, 95% CI: 1.41, 1.45; and gestational hypertension: OR=1.34, 95% CI: 1.32, 1.36). After adjustment for confounders, the associations between short interpregnancy interval and the adverse pregnancy outcomes were largely unchanged. The associations between long interpregnancy interval and the adverse pregnancy outcomes were attenuated but remained statistically significant after adjustment (eclampsia: OR=1.27, 95% CI: 1.18, 1.38; gestational diabetes: OR=1.11, 95% CI: 1.10, 1.13; and gestational hypertension: OR=1.19, 95% CI: 1.18, 1.21).

Conclusions
While short interpregnancy interval was not associated with adverse pregnancy outcomes, women with long interpregnancy intervals had statistically significant increased odds of eclampsia, gestational diabetes, and gestational hypertension. Additional studies in diverse populations are needed to confirm these findings so clinicians can aid women in optimally spacing births.

Topic: 4.14 Gestational hypertension, pre-eclampsia and eclampsia

P200 The new algorithm of clinical management for severe pre-eclampsia

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Preeclampsia is a dangerous pregnancy complication with increasing significance worldwide. The incidences of PE are 5 to 14% of all pregnancies in the world, contributes to 18% of preterm birth, and 10%-27% of global maternal deaths worldwide, while severe PE can develop to about 25 % of all cases of preeclampsia. Severe preeclampsia may lead to liver and renal failure, disseminated intravascular coagulopathy (DIC), and disorders of the central nervous system (CNS). Preeclampsia is the permanent cause of neonatal mortality and morbidity. Early optimal clinical management for severe PE at all levels of hospital care is required for better maternal as well as perinatal outcomes.

We presented the new algorithm of clinical management for severe pre-eclampsia "CALM DOWN". CALM DOWN is the special mnemonic that means "step by step strategy" for the medical teamwork. "C" is Calling for help (duty doctors and anesthesiologist with fixation of actual time). "A" is Assessment (assess the airway, auscultation, re-measure blood pressure, pulse rate, oxygen saturation, fetal heartbeats, assess the patient consciousness). "L" is Low blood pressure (antihypertensive therapy). "M" is Magnesium (intravenous therapy is with a bolus dose of diluted magnesium sulfate). Pause is evaluated on the effectiveness of prescribed medications (goal of BP < 150-160/90-100 mm Hg is recommended). "D" is Decision (decide about further management. Transfer to the intensive care unit or operating theatre or delivery room, depending on gestational age and patient`s condition). "O" is Oliguria (fluid restriction in preeclampsia is recommend no more than 60-80 mL/h of IV fluids). "W" is fetal Wellbeing (monitor fetal well-being with Doppler assessment). "N" is parturitioN (delivery is the best treatment for all women with severe preeclampsia regardless of gestational age).

We have proposed the new algorithm for medical teamwork "CALM DOWN" in the cases of severe preeclampsia that will allow systematizing and optimizing the participation of each member of the team in the provision of emergency care and improving effectiveness clinical management.

Topic: 4.14 Gestational hypertension, pre-eclampsia and eclampsia

P201 Role of 3D power Doppler of placenta for prediction of preeclampsia in high risk pregnancies

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Objectives
To evaluate the role of 3D power doppler ultrasonography of the placenta in second trimester as a screening tool for prediction of preeclampsia.

Method
A prospective observational study was conducted on 50 low risk and 50 high risk pregnant women based on age, gravidity, chronic hypertension, chronic kidney disease, SLE/APLA, diabetes mellitus and family history of hypertension. All enrolled pregnant women underwent 3D power doppler ultrasound at 18-20 weeks of gestation and again at 22-24weeks. Placental volume and vascularization indices were obtained, and vascularization index (VI), flow index (FI) and vascularization flow index (VFI) were calculated by 3D doppler histogram. They were followed till delivery and maternal and neonatal outcome were recorded and the values were compared between the high risk and low risk groups.

Results
Total 15 women developed PE, 12 from the high risk group and 3 from the low risk group. The placental vascularisation indices in women with preeclampsia had a lower VI, FI and VFI compared to those who did not developed PE and the difference was statistically significant. VI (18-20 weeks- 26.2±7.85 v/s 36.2±11.45; P=0.002, 22-24weeks- 30.4±11.1 v/s 38.6±10.1; P=0.005). FI (18-20weeks- 26.6±5.13 v/s 33.2±5.13; p<0.001, 22-24weeks- 30.4±11.1 v/s 38.6±10.1 P=0.005). VFI (18-20weeks- 7.6±1.94 v/s12.3±5.05; P<0.001, 22-24weeks- 8.4±3.75 v/s 13.1±4.73; P<0.001). At a false positive rate of 10%, at 18-20weeks the detection rates of VI was 50%. FI 59% and VFI 69%. VFI at 18-20weeks had the maximum AUC (0.851±0.040, 95% CI=0.77-0.93). Total 3 out of 15 women developed preeclampsia with severe features. Women who developed pre-eclampsia with severe features, had a lower VFI at 18-20weeks when compared to patients who had pre-eclampsia without severe features(5.6±0.35 v/s 8.1±1.84; P=0.041). Pregnancies with fetal growth restriction (FGR) showed significant difference in FI at both 18-20weeks and 22-24weeks and VFI at 22-24weeks.

Conclusion
Placental vascularisation indices are excellent predictive markers of preeclampsia. They also correlate with severity of preeclampsia and FGR. VFI at 18-20w showed the best predictive value for PE.

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P202 Screening methods in GDM according to the recommendation of the Hungarian Diabetes Association in practice

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Context

The occurrence of diabetes mellitus is steadily rising worldwide and more of a serious problem in pregnancies. Gestational diabetes mellitus (GDM) can pose severe and dangerous threats to maternal and fetal health. Later on children are at higher risk of being overweight and developing type 2 diabetes. Approximately half of the women with a history of GDM develop type 2 diabetes within five to ten years after pregnancy. For this reason besides prevention, a safe and reliable screening method should be applied. The screening recommendations highly differ in either European countries or in American Societies' opinion.

Objective

Based on the recommended screening method approved by the Hungarian Diabetes Association (MDT, Magyar Diabetes Társaság) we aimed to observe that the conducted perinatal screening was adequate to screen pregnant women. The subsequent need for insulin therapy during pregnancy was also observed in correlation of the 2 hour blood glucose levels during OGTT.

Methods

A retrograde follow-up study was conducted by comparing the results of OGTT screening 2 hour's value and birthweight.

Patients

50 pregnant women were chosen from within mothers treated in our clinic with GDM with singleton pregnancies who have participated in regular check-ups and have already given birth in term, and also 50 newborns born in term with >4000 g whose mothers had no history of gestational diabetes.

Intervention

All of the 50 pregnant mothers diagnosed with GDM were keeping a diet containing a daily 180 g carbohydrate intake, participating in regular check-ups, measuring their blood glucose levels.

Results

Only one out of the 50 treated mothers gave birth to a baby who was large for gestational age (LGA). 10 women shouldn't have been subjected to the OGTT, because their fasting glucose level was pathological. 12 mothers needed insulin treatment in some point throughout their pregnancy.
For the sake of simplicity we studied 50 newborns born in term with over 4000 g and their mothers. All of their mother's OGTT result wasn't pathological.

Conclusions

Proper care during pregnancy when GDM is diagnosed is vital, when patient cooperation is also given the results for the newborns to be born with normal birthweight are convincing. OGTT seems to be an effective screening method. It is also important that GDM isn't the only cause of LGA, genetics, the widespread use of prenatal vitamins, excessive maternal weight gain, multiparity, overcarrying can lead to the same condition.

Topic: 4.15 Gestational diabetes mellitus

P203 The prevalence of gestational diabetes in Uzbekistan

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Background

The prevalence of GDM varies in different countries from 1–18%. To date, Uzbekistan has no data on the prevalence of GDM, despite the high birth rate (more than 700,000 newborns per year).

Aims

For the first time in Uzbekistan, the goal is to study the incidence of GDM and prevailing risk factors in pregnant women in three regions of Uzbekistan – Samarkand, Khorezm, Fergana, by screening among pregnant women.

Method

In the framework of the implementation of the 3-year (2017-2020) international project "Strategy for the Prevention and Monitoring of GDM in Uzbekistan" received from the WDF Charitable Organization for Diabetes Patients UMID. GDM was screened for the first time among 1211 pregnant women 16-30 weeks gestation, aged 18-40 years. The screening included: anamnesis (presence of risk factors, number of births, etc.); anthropometry (height, weight, BMI); examination of specialists (endocrinologist, gynecologist, cardiologist); Fetal ultrasound and ECG; study of the level of glucose in the venous blood on an empty stomach and 60 minutes after OGTT (75 g of glucose). The results were interpreted according to the recommendations of IADPSG (2013).

Results

A total of 1211 pregnant women were examined in 3 regions (Samarkand - 418 women, Khorezm - 454, Ferghana - 339). OTTG conducted 898 of the total. GDM was detected in 22 pregnant women in the Samarkand region, 54 pregnant women in the Khorezm region, and 32 pregnant women in the Ferghana region. A total of 108 pregnant women with GDM were identified, which amounted to 8.9%.

In pregnant women of the Uzbek population, the following risk factors for the development of GDM were identified: age > 33 years in 23.1%; macrosomia in history (> 4kg) in 12.8%; Family history of T2D in 19.4%; overweight in 26.8% of patients; obesity in 26.8%; weight gain during pregnancy > 15-20 kg in 10.1%; miscarriages (1-3 times) in the anamnesis in 4.6%; arterial hypertension (pre-eclampsia) in 2.7%, stillbirth / non-developing pregnancy in the anamnesis in 4.6%.

Discussion. For the first time in Uzbekistan, the frequency of occurrence of GDM among pregnant women of 3 regions of Uzbekistan was detected, which was 8.9%. The prevailing risk factors for developing GDM in pregnant women of the Uzbek population were 23.1%; obesity and overweight – 26.8%; age over 33 years, Family history of Type 2 diabetes in 21 %;

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P204 Adherence to gestational diabetes mellitus screening guidelines among patients diagnosed with gestational diabetes mellitus

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Context

According to guidelines by the Polish Society of Gynecologists and Obstetricians, every pregnant woman with no pregestational diabetes mellitus should be screened for hyperglycemia in the early pregnancy with the fasting glucose plasma test (FGP). In the case of the negative results, screening with oral glucose tolerance test (OGTT) should be performed between 24th and 28th gestational week. For patients with the history of gestational diabetes mellitus (GDM), it is recommended to perform the OGTT 6-12 weeks postpartum.

Objective

The aim of the study was to asses adherence to the GDM screening guidelines during pregnancy and postpartum among GDM patients.

Methods

It was a cross-sectional study. Data was collected by means of an anonymous, electronic questionnaire distributed among patients with the history of GDM.

Patients

One hundred fifty-six patients completed the questionnaire – 89 with GDMG1 and 67 with GDMG2. Respondents were between 19 and 44 years old (mean age: 30.6 years). Twenty-six (17%) were diagnosed with obesity, 16 (10%) with insulin resistance, and 20 (12%) with polycystic ovary syndrome before pregnancy.

Interventions

The only intervention required for the purpose of this study was voluntary and anonymous completion of an electronic questionnaire.

Main outcome measure

The main outcome measure was the prevalence of FGP test and OGTT during pregnancy and postpartum among the GDM cohort.

Results

One hundred thirty-eight (88.5%) patients had the FGP test in early pregnancy. The remaining 18 (11.5%) patients had neither the FGP test nor the OGTT performed at this stage. Seventy-four (47%) patients underwent the OGTT in early pregnancy. One hundred and four (67%) patients underwent the OGTT between 24th and 28th gestational week. Fifty-six (48%) of patients who were over 12 weeks postpartum (n=116) had no OGTT performed between 6-12 weeks after delivery.

Conclusions

The most problematic areas of GDM screening identified among the GDM cohort considered postpartum care and early pregnancy.

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P205 myoinositol in treatment of gestational diabetes mellitus in Asian Indian women: a pilot study

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Context

Myoinositol is a nutritional supplement used in many insulin resistant conditions. Literature supports myoinositol in prevention of gestational diabetes mellitus (GDM). Giving myoinositol with medical nutritional therapy (MNT) soon after diagnosing GDM may improve glycemic control and reduce insulin/metformin requirement.

Objective

To compare efficacy of myoinositol with medical nutrition therapy (MNT) vs. MNT alone for treatment of GDM in Asian Indian women.

Methods

This pilot randomized controlled trial was registered with the Clinical Trial registry of India CTRI2018/05/013937 and conducted after ethical approval.

Patient(s)

100 antenatal patients with singleton pregnancy with GDM diagnosed between 12-28 weeks gestation were included. Overt Diabetes, twin pregnancy, pre-existing renal disease, heart disease and other chronic medical disorders were excluded.

Intervention: Patients were randomized in two groups by opaque envelope method. Group-1(n=50) received Myoinositol 1000 mg+ Folic acid 0.5mg, twice daily along with MNT; Group-2 received only MNT with Folic acid 0.5 mg, twice daily. Both groups were given iron, calcium and Vitamin D3 as part of regular ANC care. Patients were then followed with 4-point blood sugar monitoring 2 weekly.

Main outcome measure(s)

Primary outcomes measure was glycemic control as monitored by 4-point blood sugar profiles and percentage reduction in need of additional pharmacologic therapy.

Result(s)

Baseline risk factors for development of GDM were comparable in both groups. In group-1, glycemic control was achieved in 89.8% patients which was higher than group-2 (68%)(p 0.008). Need for additional treatment with insulin or metformin was lesser in Group 1 vs. Group-2 (5/49 vs. 16/50 respectively)(p=0.08). The median dose of insulin was 19 units in cases(range-16-41) compared to 12 units (range 5-27) in the controls though the difference was statistically not significant (p=0.192). Baby weight was higher in Group-2(3036 gm) as compared to Group-1(2820 gm) (p 0.018).

Conclusions

Oral supplementation with myoinositol in dose of 1 gm twice daily, when started soon after the diagnosis of GDM, is effective in achieving glycemic control and decreasing the need for additional pharmacological therapy as compared to controls in Asian Indian women. Myoinositol offers advantage over insulin in its oral route, good safety profile in pregnancy, minimal gastrointestinal side effects and good patient tolerance.

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P206 Fasting C-peptide and Insulin Resistance/ Sensitivity in Gestational Diabetes Mellitus

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Context
Defective insulin secretion and/or insulin action are two characteristics of Gestational Diabetes Mellitus (GDM) that are not settled and remains matter of controversy as yet.

Objectives
To see C-peptide and insulin indices in homeostatic model assessment in GDM.

Methods
Glucose was measured by glucose oxidase method, insulin by ELISA and C-peptide by immunochemiluminescent methods whereas insulin indices were calculated by using HOMA-IR, HOMA-B and HOMA-%S.

Patients
This study encompassed 120 pregnant women irrespective of age of gestation divided into GDM (n=64, age: 27.02 ± 4.26 years, BMI: 26.38+4.75 kg/m^2; mean±SD) and normal glucose tolerance (NGT; n=56, age: 26.11±4.13 years, BMI: 24.38+3.59 kg/m^2; mean±SD) on the basis of WHO 2013 criteria for diagnosis of GDM.

Interventions
Cross-sectional, observational study

Main outcome measures
C-peptide level and insulin indices

Results
Out of 120 C-peptide was below the detection limit (< 0.10 ng/ml) in 58 mothers. C-peptide non-significantly whereas fasting insulin significantly (10.57+1.09 vs 7.68+0.56; p= 0.039) were higher in GDM than those of NGT. Mothers having C-peptide <0.1 ng/ml had FPG lower than that in mothers having detectable C-peptide (4.7 + 0.57 vs 5.05+ 0.74 mmol/L; p=0.005). HOMA-IR (GDM vs. NGT; 2.24+1.36 vs. 1.49+1.03, p=0.001) was higher whereas HOMA-B (GDM vs. NGT; 120.56+83.40 vs. 180.64+ 169.19, p=0.013) & HOMA-S (GDM vs. NGT; 61.78+38.57 vs. 122.69+186.13, p=0.012) lower in GDM than those of NGT. Neither C-peptide nor fasting insulin differ significantly among trimesters within each group or between GDM and NGT in any trimester (p=NS for all comparisons). Circulating concentration of C-peptide (BMI <23 vs. BMI ≥23 kg/m^2; 0.185 +0.06 vs. 0.331+0.44 ng/ml, mean±SD; p=0.028) was significantly lower in GDM with low BMI. BMI showed positive correlation with fasting insulin in both GDM and NGT groups (r=0.369, p=0.019; r=0.412, p=0.008; respectively) as well as with HOMA-IR (r=0.324, p=0.041; r=0.415, p=0.009; respectively). Analyses with covariates revealed BMI (p=<0.007) and HOMA-B (p=0.006) as independent predictor over the glycemic abnormality.

Conclusion
Fasting C-peptide do not differ significantly between GDM and pregnancy NGT. However, insulin resistance is higher in GDM which is also true even when there is minimally undetectable secretion of C-peptide by pancreas in the face of abnormally higher glucose in GDM.

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P207 Metformin administration during pregnancy- current insight

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Context
Because the main mechanism of gestational diabetes mellitus (GDM) is insulin resistance, using metformin as a medicine which reduces insulin resistance appears to be promising.

Objective and Methods
In this poster, the authors attempt to discuss the use of metformin during pregnancy and the safety of the treatment in the light of current studies and recommendations.

Results
Currently, the majority of medical associations do not recommend using metformin during pregnancy as the first-line therapy when the diet regimen is insufficient for glycaemic control. However, they do allow its administration if there is no possibility of insulin treatment.
There is some evidence which suggests that using metformin during pregnancy is not related to an increased risk of obstetric complications during delivery and that its influence on the foetus can be beneficial.

Conclusions
Since metformin crosses the placenta the major argument for cautious use of this drug are the potential long-term effects of the treatment for the child and its development in later life.

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P208 Gestational diabetes mellitus – to metformin or not to metformin?

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Background

Gestational diabetes mellitus (GDM) is an independent risk factor for obstetric complications. The primary goal in GDM treatment is to maintain normoglycemia. If there is a need for pharmacologic treatment, the primary choice is insulin, proven to be safe and effective alternative as it does not cross the placental barrier and has no teratogenic effect. Of the oral hypoglycaemic agents, metformin is one of the well-studied for the treatment of GDM. Nevertheless, the use of metformin during pregnancy has encountered conflicting opinions.

Aim

The aim of the present study was to asses whether there are differences in maternal and fetal anthropometric and biochemical parameters in pregnant women with GDM treated with metformin compared to those treated with nutrition therapy or insulin.

Materials and methods

We have performed a single center, retrospective study using the electronic database of "Dr Shterev" Hospital. The analysys included data of 238 pregnant women with GDM, diagnosed by an oral glucose tolerance test (OGTT). Patients were divided into three groups, depending on the treatment regimen - diet (n=123), metformin (n=75), insulin treatment (n=40 women). Only women who did not change the therapeutic strategy until the end of pregnancy were included in the observation. We have analysed the mean age, body mass index of women, mean serum fasting blood glucose levels, glycated hemoglobin and blood pressure, measured at the moment of diagnosing the GDM, and at the end of pregnancy; the birth method, and newborn parameters such as birth weight, BPD, Apgar score. The groups were compared using Mann-Whitney U-test.

Results

Patients needed pharmacological therapy showed significantly higher baseline BMI, mean serum fasting blood glucose concentrations and glycated hemoglobin ($p<0.0001$). However, in the course of pregnancy, patients treated with metformin, showed lower mean BMI ($p<0.0001$), lower fasting glucose levels and lower levels of glycated hemoglobin. No difference was observed in the analyzed parameters of the newborns in the three groups.

Conclusion

The results of this pilot retrospective series reveals that patients with GDM with higher baseline BMI have a need to add pharmacological therapy to maintain euglycaemia. Patients treated with metformin have a more favorable profile for all the follow-up variables. No short-term complications have been observed in neonates among women treated with metformin.

Topic: 4.15 Gestational diabetes mellitus

P209 Potential role of the biochemical placentation markers PAPP-A and hCG for early gestational diabetes screening - a pilot study

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Background

The gestational diabetes mellitus (GDM) is one of the most common pregnancy complications. The universal screening is usually conducted between 24th and 28th gestational weeks. In case of diabetes, this often delays the diagnosis and could potentially augment the risk of unfavourable pregnancy outcomes. Some of the biochemical placental markers, used in the universal screening for aneuploidy, probably could also yeld a diagnostic value for GDM - pregnancy associated plasma protein A (PAPP-A)and human choriongonadotropin (hCG).

Aim

To elucidate if PAPP-A and hCG values were different among pregnant women with and without GDM and respectively to test its place in the early gestational diabetes screening

Patients and methods

We have performed single center, retrospective study using an electronic database of "D-r Shterev" Hospital. The analysys included data of 125 pregnant women with GDM and 138 pregnant women without disturbances of the glucose homeostasis, served as a control group. The gestational diabetes in the study group was diagnosed by a oral glucose tolerance test (GTT). We have analysed the mean serum levels of PAPP-A, hCG, fasting glucose (FG), and body mass measured between 10 and 13 gestational weeks. Serum levels of PAPP-A and hCG are presented as multiples of the normal median (MoM), adjusted by maternal baseline characteristics and demographics. The groups were compared using Mann-Whitney U-test.

Results

In patients who developed GDM during pregnancy we have found significantly lower multiples of the normal median values of PAPP-A ($p<0,0001$), higher values of fasting glucose ($p<0,05$) as well as higher BMI ($p<0,0001$). The multiples of the normal median of the hCG were similar in both group of pregnant women (p= ND).

Conclusion

The results of these pilot retrospective series reveals that low normal to low reference range values of PAPP-A might indicate increased risk of development of GDM. As PAPP-A is a part of a routine early screening program in Bulgaria, further prospective studies should be planned to reveal the sensitivity, specificity and predictive value of low-normal PAPP-A for GDM later during pregnancy.

Topic: 4.16 Normal and abnormal intrauterine growth

P210 Maternal folic acid intake and methylation status of ventricular septal defects (VSD) associated genes in children: cases and controls

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Context

DNA methylation is the best characterized epigenetic mechanism to explain the interactions between nutrients and genes involved in intrauterine growth and development programming. A possible contribution of methylation abnormalities to congenital heart disease is the folate methylation regulatory pathway, however the mechanisms and methylation patterns of VSD associated genes are not fully understood.

Objective

To determine if maternal dietary intake of folic acid (FA) is related with methylation status (MS) of VSD associated genes (AXIN1, MTHFR, TBX1 y TBX20).

Methods

Pilot-exploratory, cross-sectional, observational, descriptive study. 32 mothers and their children were evaluated (16 cases and 16 controls). Mothers, dietary variables were collected through a food frequency questionnaire with FA and consumption of supplements with FA; clinics (presence of maternal diabetes mellitus, exposure to medications during pregnancy) and drug addiction (alcoholism). The presence of VSD, family background and MS (qPCR was used to estimate the methylation level of AXIN1, MTHFR, TBX1 y TBX20 gene promoters whit Sybr Green specific primers) were determined from the children. Statistical analyzes were performed in the SPSSv.22 software.

Result(s)

Cases: 56.3% were men and 43.8% women. Higher maternal age was observed in children with VSD but without significant differences (25.22±7.21 vs 21.22±42.86; p=0.151). Maternal FA dietary intake was similar in both groups (p=0.474); in addition, 31.3% of mothers with VSD children reported not to consume FA supplements observing significant differences (p=0.015). Significant differences were observed in the MS of AXIN1, MTHFR and TBX20 genes between healthy children vs children with VSD (100±24.21 vs 68.7±23.83, p=0.001; 3.08±2.39 vs 9.78±8.09, p=0.001; 4.25±2.74 vs 7.83±5.22, p=0.021, respectively). Also correlation between maternal FA supplementation and methylation status VSD associated genes in healthy children vs VSD children were reported (AXIN1: 100±24.21 vs 66.03±25.57, p=0.002; MTHFR: 3.08±2.39 vs 10.71±939, p=0.023 and TBX20: 4.25±2.74 vs 7.42±4.41, p=0.029).

Conclusions

Consumption of FA supplements and MS of VSD associated genes were different between cases and controls, in addition, FA maternal supplementation was correlated with the MS of AXIN1, MTHFR and TBX20 genes. Although no significant differences were observed, there is a tendency towards higher maternal age in children with VSD.

Topic: 4.16 Normal and abnormal intrauterine growth

P211 Evaluation of cases of molar pregnancy - a prospective observational study

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Aims and objectives

The study was undertaken in the department of Obstetrics & Gynecology, Kamla Nehru State Hospital for mother and child (KNH), Indira Gandhi Medical college, Shimla, Himachal Pradesh, India. The aim of the study was to estimate the incidence of molar pregnancy and to evaluate the risk factors of molar pregnancy.

Methods

A total of 57 patients with molar pregnancies were diagnosed and enrolled for the study conducted over a period of 1 year (1st March 2012 to 28th February 2013). Statistical testing was conducted with the statistical package for the social science system (SPSS) version 17.0. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate.

Results

The incidence of molar pregnancy was 3.4 per 1000 pregnancies. Out of total 57 cases, 49(85.96%) were of complete H mole and 8(14.03%) were of partial H mole. Majority of the patients [24/57(42.1%)] were in the age group of 20 – 25 years. 4 out of 57 molar pregnancy patients (7.01%) and 3 out of 16298 women with normal pregnancy, had history of molar pregnancy (0.02%) and the difference was statistically significant. 29 out of 57 (50.87%) patients of H mole belonged to class 4 (upper lower) SES. Molar pregnancy was more common in multipara. 41out of 57 (71.9%) patients had size of uterus more than the period of gestation. There was a highly significant relationship between presence of theca lutein cysts and β HCG levels > 1,00,000 IU/l. 3 (5.3%) patients developed GTN out of which one (1.8%) patient developed choriocarcinoma. 2 (3.5%) other patients of GTN had invasive moles. There was a statistically significant difference between the β HCG levels of those patients who required an additional treatment and those who did not require any additional treatment. All the 6 patients belonging to the high risk group subsequently required chemotherapy.

Conclusion

H mole is one of the important causes of maternal morbidity. Extremes of maternal age and previous history of H mole are important risk factors of molar pregnancy. H mole is also more commonly seen in multiparous women and women of lower SES. Early diagnosis in patients of H mole with USG is beneficial for the patients as they get definitive treatment earlier. By regular follow up, prognosis of GTN can be improved by early diagnosis and early administration of chemotherapy. This is possible only by raising awareness regarding the malignant potential of GTD.

Topic: 4.16 Normal and abnormal intrauterine growth

P212 Meta-analysis regarding the effect of milk consumption during pregnancy on fetal growth and obstetric outcomes

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Background

Milk is a source of proteins and micronutrients, although results regarding the effect of consuming it during pregnancy on fetal growth and development are controversial.

Aim

To perform a systematic review and meta-analysis to compare pregnant women consuming nil or a minimal amount of milk and/or related products as compared to consuming higher quantities.

Method

Searches were performed in PubMed, Scopus, Web of Science, EMBASE, and Cochrane Library reporting fetal measures and clinical outcomes in order to evaluate the association between milk and related derivatives on fetal growth. Random effect models and inverse variance were used for meta-analyses. Summary measures were mean differences (MDs) and odds ratios (ORs) with 95% confidence interval (CI). Risk of bias was evaluated with the Newcastle-Ottawa Scale.

Results

Pooled analyses of seven studies revealed a positive effect of higher milk consumption during pregnancy on birthweight (MD=69.8 grams, 95% CI 42.1-97.4) and head circumference (MD=0.12 cm, 95% CI 0.01-0.23, n=3 studies). In addition, high milk consumption is associated with a reduced risk of small-for-gestational age (OR=0.65, 95% CI 0.49-0.85) and low birthweight infants (OR=0.51, 95% CI 0.37-0.72).

Conclusion

This meta-analysis evidences that milk consumption during pregnancy was associated to an objective increase in infant birthweight and a reduction of negative clinical outcomes.

Topic: 4.17 Infectious diseases and pregnancy

P213 Congenital early syphilis

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Context

Early congenital syphilis is a multi-systemic infection caused by Treponema pallidum, which reaches the fetus after passing through the placental barrier. In recent decades, the number of cases have fallen, yet children are still born with congenital syphilis. Diagnosis can sometimes be difficult, while clinical appearances occur depending on the time the infection occurs. Early detection of the disease is particularly important, as congenital syphilis is one of the few transplacental infections for which effective treatment is available.

In Bulgaria pregnant patients undergo routine serological screening for syphilis. In Pleven region of Bulgaria, there are 8544 patients examined for a five-year period. From those patients there were 2 % (144 cases) with different prescription of newly developed and/ or newly diagnosed syphilis.

According to the data from the National Center for Public Health and Analysis of Bulgaria in 2014 there were 26 reported cases of early congenital syphilis, while 5 cases were reported for the period March 2018 – April 2018.

Objective

The aim of the study is to emphasise the need of adequate prenatal care in every pregnant patient.

Patient

Presenting a case of a multipara woman (G7,P5) at seventh month of gestation who did not attend any previous examinations.

Interventions: The patient is admitted in the labour ward for a delivery of a stillbirth that was recently diagnosed. After a serological examination, a clinic for fresh secondary syphilis was established with characteristic exanthem and enanthem and highly positive serological tests: VDRL / 4 + /; TPHA / 4 + /; IgM / IgG positive ELISA.

Results

Stillbirth (28th gestational week) due to congenital early syphilis, terminated by a 1350 grams neonate with severe hydrophobia and maceration, multiple organ failure, specific histopathological data for intrauterine infection: brachycephaly; flat face and rear; horizontal eyes; low inserted ears; split upper lip; wrist subluxation.

Conclusions

Prophylaxis of congenital syphilis from the routine serological examination of pregnant women during the first prenatal visit is a step towards a more favorable outcome of pregnancy. In more advanced stages of the intrauterine development of congenital syphilis, fetal morphology can detect many pathological findings that require direct attention.

Topic: 4.17 Infectious diseases and pregnancy

P214 Correlation between Candida spec. infection and imminent abortion

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Context
The term threatened abortion is used when there is vaginal bleeding prior to 20 weeks gestation. This may be accompanied by abdominal aching or cramping. Upon vaginal examination, the cervix is found undiluted. Incidence is 25% of pregnant women experiencing some quantity of vaginal bleeding; of these, 50% ultimately miscarry. When there is threatened abortion caused by a number of factors, including hormonal dysregulation or vaginal infection. In pregnancy, higher levels of estrogen make a woman more likely to develop a yeast infection. During pregnancy, the Candida fungus is more common, and recurrent infection is also more likely

Objective
Our purpose was to investigate the putative association between candida spec. infection and imminent abortion.

Methods
Cervical samples were obtained from 286 patients, from whom 89 were women with idiopathic recurrent spontaneous abortion, 95 were women with normal pregnancy and 102 were women with imminent abortion. Cervical samples were investigated for presence of candida spec.

Patients
About 286 pregnant women were studied in a randomized selection.

Results
22 women with recurrent spontaneous abortion {24.7%} were candida spec. positive, compared with 20 patients with normal pregnancy [21.1 %] and 40 fertile women with imminent abortion [39.2%]
Prevalence of candida spec. infection in the group of women with imminent abortion was significantly higher than in the other groups, who were control groups [p<0,001 and P<0.05,]
On the basic of those results we can conclude that candida spec. infection plays an important role in etiology of imminent abortion.

Key words: candida spec. infection, imminens abortio

Topic: 4.17 Infectious diseases and pregnancy

P215 Genital infections and chorioamnionitis - diagnosis and management

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Chorioamnionitis or intraamniotic infection is the infectious process that affects intrauterine content during pregnancy and it is a common complication during pregnancy. We want to present a numerous studies who reported vaginal colonization with Group B Streptococcus, Escherichia coli, Gardnerella vaginalis and sexually transmitted infections as risk factors for chorioamnionitis. Also, chorioamnionitis can apper to the pacient with intact membranes with fastidious genital mycoplasmas such as Ureaplasma species and Mycoplasma hominis, who is found in the inferior genital tract in 70% of women. Although this complication occurs due to the ascending polymicrobial bacterial infection at the time of membrane breakage, it may also occur in pregnant women with intact membranes. Chorioamnionitis should be suspected in pregnant women with one or more of the following signs: fever over 37.8° C, maternal and/or fetal tachycardia, purulent leukorrhea, maternal leukocytosis. If fever persisting more than an hour, the pacient need a new evaluation and appropriate intervention. Fetal complication can be pneumonia, sepsis, fetal death, intraventricular hemorrhage. International guidelines recommend double association of Ampicillin or Cefazolin or Clindamycin with Gentamycin. Interestingly, although the syndrome is frequently associated with Ureaplasma and Mycoplasma hominis, the standard antibiotic regimens recommended are not effective on all ureaplasma species. In conclusion, this may suggest to need the new studies confirming that diagnosis and treatment according to the antibiotic of vaginal infections for Ureaplasma and Mycoplasma hominis in the first trimester of pregnancy could prevent chorioamnionitis. The correct management of clinical chorioamnionitis includes antibiotic therapy and delivery.

Topic: 4.17 Infectious diseases and pregnancy

P217 Challenges in the management of HIV positive pregnant women in a Romanian Hospital

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Human immunodeficiency virus (HIV) is a Lentivirus that causes AIDS (Acquired immunodeficiency syndrome). The actual incidence of HIV positive pregnant women in our country remains unknown. A HIV positive women's pregnancy represents a challenge for the obstetrician and for the infectious disease doctor.

Objective

The purpose of this study was to evaluate the incidence of HIV positive pregnant women in our hospital (Cuza Voda Iassy Maternity), the maternal and foetal complications and possible particularities that will help us have a better management regarding this pathology.

Methods

We have conducted a retrospective study from 2013 until 2018. We have studied all the medical documents of these HIV positive pregnancies both the mothers and the new-borns.

Results

The age of most cases was between 20-30 years and they were from Iassy county. HIV positive birth incidency was under 0.3%. 20.68% from our patients gaved birth prematurely. Impaired intrauterine foetal growth was higher in the cases with antiretroviral therapy preconceptionally. Hepatitis coinfection was frequent.

Conclusions

We have observed a low incidence of HIV positive births in our hospital, with most of the cases coming from rural areas. A high proportion of these births had complications. It becomes obvious that the severity of the infection negatively influences the evolution of the pregnancy. In cases with monitored pregnancy the evolution had less complications. To obtain a lower vertical transmission rate we need to increase patient's addressability to health care services regardless of costs and social stigma.

Topic: 4.19 Labor induction

P218 The efficiency of Laminaria as an adjunct to induction of labour with prostin: a randomised controlled trial

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Introduction

Prostin (Prostaglandin E2) is an established agent for induction of labour (IOL). Laminaria has also been shown to be an effective mechanical agent for induction of labour. There is limited data on using Laminaria as an adjunct before Prostin in IOL.

Objective

This study was conducted with the aim to investigate whether laminaria insertion prior to prostin would improve the success rate of induction of labour by reducing the need for and number of Prostins required, shortens the interval to active phase of labour, shorten the duration of labour, and to investigate the maternal and fetal outcomes of labour.

Methodology

This is a randomised controlled trial, where 160 patients admitted to a tertiary centre for IOL were recruited and randomised to two groups: Group A(study group) was the Laminaria group where Laminaria was inserted before prostin insertion and Group B (control group) where only Prostin was used for IOL. Statistical significance was calculated using the Chi-square test when comparing qualitative data and student t-test for comparing quantitative data with a p-value of less than 0.05 was taken as significant.

Result

The average Bishop score in both groups at the time of admission was 4.0. In group A, after laminaria insertion, 14(17.5%) of patients went into the active phase of labour without requiring prostin at all compared to only 4 (5%) participants in the control group ($p = 0.02$). The treatment group demonstrate shorter time to achieve the active phase of labour with a mean time of 338.25(±24.27) minutes compared with the control group with mean time of 518.44(±34.17) minutes (p-value <0.001). The success rate of IOL was 92.4% and 93.4% in group A and B, respectively.

Conclusion

The use of Laminaria as an adjunct to prostin in the induction of labour increases the success rate of IOL without increasing the duration of hospital stay and only a minimal increase in overall cost.

Topic: 4.19 Labor induction

P219 Efficacy and safety of prostaglandin E2 (PGE2) for labor induction

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Introduction

Induction of labor is the most common intervention in obstetric practice, the attitude to which is still controversial. The lack of consensus on the use of labor induction in obstetric practice in general, objective evidence of the advantages of some methods over others, in particular, helps to maintain the relevance of this problem.

Objective

To evaluate the clinical course of labor induction depending on the method of delivery in comparison with the clinical course of spontaneous labor.

Materials and research methods

A retrospective analysis of 111 cases of women were carried out. All patients had delivered in the clinic of the Republican medical center of Obstetrics and Gynecology in the period from April to October 2018. The main group included 81 women with induced labor at 35-42 weeks of gestation. The labor was induced with synthetic prostaglandin E2 - dinoprostone. The control group included 30 women with spontaneous delivery at 37-42 weeks of gestation.

Results of the study

The average age in the control group was 25.5 ± 1.2 years, and in the main group 24.2 ± 1.3 years. Among women in the control group the primiparas were 21 (70%) patients, and multiparous - 9 (30%). Whereas, in the main group - 51 (62.9%) and 30 (37.1%), respectively. Indications for the labor induction were: the gestational age 41-42 weeks, placental insufficiency with fetal growth restriction 1-2 degree, as well as the "immature" cervix - 1.4 (0-2.5) points on the Bishop-Golubev scale. The absence of the effect of labor stimulation and delivery by cesarean section was observed in 3 patients of the main group. The active phase of delivery in the main group developed after 75.9 ± 3.5 minutes. The duration of labor in the main group was 326.6 ± 4.5 minutes, while this indicator was less than the average duration of labor in the control group - 441.0 ± 3.5 minutes. In the postpartum period, there were no complications in the puerperas of the main and control groups as well.

Conclusions

The proposed induction method is most effective in labor excitation, since it did not require additional use of other induction methods. An emergency cesarean section due to the absence of the effect of labor stimulation was significantly more often performed using induced labor. Labor activity during induction requires more support with uterotonics than in spontaneous ones. Induced contractions are more painful than physiological ones.

Topic: 4.19 Labor induction

P220 Prognosis of labor induction

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Introduction

Nowadays, programming delivery was created as an optimal technology.

Objective

Evaluation of various methods of labor induction.

Materials and methods

The following methods of labor stimulation were used. Instrumental methods include amniotomy. Medical: dinoprostone in combination with NO donor L-arginine - Tivortin. Dinoprostone was prescribed vaginally to all pregnant women of the main group in order to ripen the cervix. Prior to insertion of Glandin, were used NO-donor Tivortin in a dosage of 100 ml i/v, drip slowly 60 minutes before the start of induction. A prospective analysis of the course and outcome of labor induced by various methods was performed in 120 women with a gestational age at the time of induction 36 - 42 weeks.

Results

After statistical processing of the data and analysis of the results, a point scale for labor stimulation was proposed: parity (1st - 0 points, 2nd - 1 point, 3 or more - 2 points); age (21-30 years - 1 point, 31-37 years - 0 points, 37 years and older - 2 points), gestational age (up to 279 and from 284 days - 0 points, 280–283 days - 1 point); Cervical maturity by Bishop scale and fetal condition as a risk factor for cesarean section (pathology - 0 points; normal - 1 point). Based on a step-by-step analysis, two equations were derived for logistic regression using the first stage of analysis (4 factors: scale, mifepristone, dinoprostone, amniotomy — y1 value) in formula 1:

y1 = 6.577 - 1.088 * Sca - 0.83 * Mif - 0.647 *

Din + 0.79 * Amn (1)

Sca - points on the scale;

Following, on the 4th (taking into account only the scale - y4 - formula 2):

y4 = 4.914 - 0.88 * Sca (2)

Substituting the point on the scale in both equations, we get y1 and y4 for each woman we have been studied. The induction coefficient - 1 takes into account not only a point on the scale, but also the methods of induction of labor, which allows you to evaluate the pregnant reaction to delivery and the woman's ability to give birth naturally or not. The induction coefficient - 4 - only a point on the scale, which is necessary to determine the need for a woman in induction.

Conclusion

Thus, formulas (1) and formulas (2), allows to obstetrician-gynecologist quickly evaluate the potential response of the pregnant woman for delivery by y1 and her need for induction by the second formula y4 during the initial examination. Mentioned above makes it possible to reduce the time for making decision and simplifies the medical diagnostic process.

Topic: 4.19 Labor induction

P221 The utility of ultrasound examination in the surveillance of Misodel induced labor

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Introduction

Misodel (misoprostol) is an E1 prostaglandin that is most frequently used in obstetrics for the induction of labor. Its action consists in raising the hydration level of the cervix, and by this inducing cervical ripening, with its consecutive effacement and dilatation.

Objectives

The main purpose of the study was to determine the efficacy and safety of prescribing misodel for the induction of labor and also to objectify its effects upon the cervix trough seriated transvaginal ultrasound examinations.

Material and methods

The study included 211 pregnant women, of which 122 were primiparous and 89 multiparous, whom they were administered Misodel for the induction of labor. Amongst the tracked parameters, we mention the length of the cervix, measured every hour since the moment of the device insertion and until the beginning of labor, the fetal and maternal intrapartum condition, the rate of emergency C-section, and also the Apgar score and the need of fetal intensive care.

Results

The amount of time elapsed from the moment of the device insertion until the beginning of the labor ranged between 3 and 24 hours, with an average lapse of 8-12h for primiparous women and 3-8h for multipaous women, during which we performed endovaginal ultrasound examination, for the assessment of the cervix length.

Conclusions

The inducing of labor and labor itself can be a long and extremely tiring experience for the pregnant woman. The use of misoprostol showed its benefits in shortening the labor period, with a significant decrease in the amount of time needed for the shortening, effacement and dilatation of the cervix, objectified trough endovaginal ultrasound examination, with a low rate of fetal distress.

Topic: 4.19 Labor induction

P222 Labor induction in high-risk pregnancy with misoprostol – our experience

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Contex
Gestational hypertension remains the leading cause of maternal, fetal and neonatal morbidity and mortality worldwide, this being the most common medical disorder complicating pregnancy.
In order to prevent the development of severe preeclampsia, HELLP syndrom, eclampsia and adverse fetal outcome labor induction is recommanded in patients with gestational hypertension > 38 weeks.

Objective
To assess the obstetrical outcome in pregnancies with gestational hypertension after labor induction with misoprostol and compare the off-label administration of misoprostol versus the vaginal delivery system.

Method
We performed a retrospective study of primipara 38 weeks and Bishop score < 6 with gestational hypertension that were subjected to labor induction. Patients were divided according to the type of misoprostol administation: 18 patients received the vaginal delivery system and 24 received the off-label misoprostol tablets. All patients were admitted in the labor ward, complete blood and urine analisys were performed, the usual antihypertensive medication was continued, all patients received epidural anesthesia, continuous electronic fetal monitoring was done and active management of 3rd stage of labor was performed. Pregnancies complicated with severe fetal growth restriction, BMI > 35 and preexisting diabetes were excluded.

Results
The success rate of labor induction in terms of achieving vaginal delivery with misoprostol vaginal delivery system was 87% and with off-label medication 68%. The Apgar scor was similar in both groups, as well as the NICU admisson.

Conclusions
Misoprostol as a vaginal delivery system was more efficient in labor induction in our high-risk pregnancy patients than the off-label medication. Pregnancy outcome was comparable in the two groups, so both types of misoprostol administration were safe.

Topic: 4.20 Caesarean section: pro and con

P224 Uterine isthmocele - a late complication of cesarean delivery

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Context

In the late decades, the incidence of caesarean delivery has constantly increased due to various factors. Until recently, the importance of a uterine scar was taken into consideration only in pregnancies where complications like adherent placenta, uterine dehiscence or rupture or scar pregnancy were definitely related to a previous cesarean section. Isthmocele is a new pathology strictly related to uterine scar that should be considered as a late complication of a cesarean delivery. There are different methods used in evaluation of the uterine scar, ultrasound being an important and unexpansive tool that requires no special preparing.

Objectives

We tried to evaluate the correlation between severity of the symptoms possible related to isthmocele and the ultrasound findings.

Results

The most frequent symptom was represented by abnormal uterine bleeding. It usually appeared 1-2 years after the C-Section. It was usually described as a reddish-brown postmenstrual vaginal discharge. The most frequent sign was a hypoechoic area at the level of the uterine scar. The dimensions vary from 0,2 mm to 1-2 cm. There were cases when the whole uterine wall was affected, the isthmocele being categorized as “a large” one. The dimensions of the uterine wall defect did not corelate with the degree of the bleeding.

Another symptom was chronic pelvic discomfort. In cases where the uterine wall defect was present and the structural causes were eliminated (cysts, fibroids a.s.o.), the ultrasound revealed other possible causes for chronic pain, like pelvic adhesions or pelvic vessel distensions. The isthmocele itself did not seem to be the only one responsible for the discomfort.

Conclusion

Although a benign disease, the uterine niche can modify the normal function of the female genital tract with consequences on the quality of life. The pathology is strictly related to the C-Section scar, with potential long-term morbidity. It is important to note that treatment should be taken into consideration only in cases with evident discomfort, but the preventive strategy, like a reduction in the C-Section rate, should be also taken in account.

Topic: 4.21 Fetal origins of adult diseases

P226 Aplasia cutis congenita – case report

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Introduction

Aplasia Cutis Congenita (ACC) is a heterogeneous group of rare, congenital disorders that demonstrate focal or diffuse absence of skin mostly on the scalp, but may occur anywhere on the body. Few of the scalp cases may be accompanied by underlying bone and dura mater defect, with possible extension to the brain and sagittal sinus. In most cases ACC is isolated, although it has been associated with various syndromes and congenital anomalies. Incidence is 1-3:10,000 live births. Sporadic ACC is most prevalent, but familial cases have also been reported.

Material and Methods

At a planned Cesarean delivery in 39 week of gestation, a girl was born with weight 3460 grams, height 51 cm and APGAR score 7, 8, 9. The indications for Cesarean delivery were signs of fetopelvic disproportion and myopia. Through the pregnancy the woman was taking only vitamins and iron supplements. During the delivery procedure we noticed a 2 cm round lesion on the head of the baby, specifically at the vertex part. The baby was otherwise healthy, in good condition with no signs of other malformations. CT scan was performed to reject other possible conditions. The conclusion of the CT scan was: Normal CT status. Small intradermal fibrosis occipitally in the left. No changes of the structure of the skull bone and the brain tissue. Later the grandmother reported that she also had a Cesarean delivery and her baby (our patient who gave birth) was born with a similar lesion on the skin of the head, then it was considered of iatrogenic origin. It healed spontaneously and nowadays, the mother has a small scar in the vertex part of her head.

Results

After rejecting all other possible conditions, the baby was diagnosed with ACC type I. Conservative approach was considered. At the 4th postnatal day, the lesion was healing well and fresh granulation tissue occurred. The mother and the baby were discharged at the 6th day with a visible improvement in the lesion's condition.

Conclusions

There is no consensus about the management of ACC cases. The decision for conservative or operative treatment usually depends on the size of the lesion and the risk of infection or bleeding. Conservative management include local wound care and administration of systemic antibiotics. Surgical treatment is performed when there is a big skin defect. It includes primary wound closure, skin grafts and local flaps. In our case, the conservative approach resulted in fast improvement of the lesion.

Topic: 4.21 Fetal origins of adult diseases

P227 Fetal hepatosplenomegaly discovered after delivery – case report from Clinical University Center of Kosovo

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Context
Hepatosplenomegaly is the simultaneous enlargement of both the liver (hepatomegaly) and the spleen (splenomegaly). Hepatosplenomegaly can occur as the result of acute viral hepatitis, infectious mononucleosis, and histoplasmosis or it can be the sign of a serious and life-threatening lysosomal storage disease.

Objective
The aim of this study is to clarify that the follow up examinations by an obstetrician can lead to an early diagnosis of fetal hepatosplenomegaly and early diagnosis and treatment of children who have liver disease is important because specific treatments are available for some diseases that can prevent disease progression or hepatic failure.

Methods
This study is a case report study of a single patient that was hospitalized in Clinical University Center of Kosovo QKUK in December 2019 and delivered her baby at 34 weeks of gestation. Patient Patient A.F 18 years old blood group 'A-Rhd Positive, was hospitalized in Clinical University Center of Kosovo. The patient came in to the hospital with severe labor pain complaints and was immediately was sent to the labor room after the gynecological examination and concluded that her cervix was 8 cm dilated. After several minutes she gave birth to a male baby. She didn't follow her pregnancy regularly with an obstetrician due to her economic reasons. Such so the doctors before delivery asked for TORCH analysis to be done. Before she found out she was pregnant she admitted that she smoked tobacco regularly and and drank alcohol time to time. She continued smoking tobacco regularly during her pregnancy too.

Main outcome measure
The delivery took place at 34 weeks of gestation, the baby had yellow skin, a swollen abdomen, tenderness in the right region of abdomen, could not adapt its body temperature due to fever and respiration problems, Its weight was about 2190 gram with an Apgar Score of 5/7. The fetus was sent to incubator and was monitored for several weeks.

Results
The mom is in healthy condition in the other hands the baby's health condition is still monitored and its analysis are regularly being asked. The body temperature regulation is being controlled in the same time further examinations are being done. Baby has typical jaundice and yellowing of the eyes and skin.

Conclusions
In conclusions we think that this study will arouse the right institutions to prevent such cases and show that regular check ups are important.

Key words: Fetal hepatosplenomegaly, Kosovo, obstetrics

Topic: 4.22 Postpartum management of high risk pregnancies

P228 Subcapsular hepatic hematoma - a complication of HELLP syndrome - a case report and literature update

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Subcapsular hepatic hematoma is a rare complication of HELLP syndrome, an unusual clinical phenomena that can occur during pregnancy and childbed, that can set off a series of critical complications regarding the fetal and maternal mortality. This is a case report of a 33 years old woman, gravida 3, parity 3, with a 38 week pregnancy, without any medical observation during pregnancy, with no pathological history, that gave birth to a living, 2650g, Apgar 9 infant. One hour postpartum, she complained about pain located in the right shoulder, dyspnea, orthopnea, psychosomatic anxiety and the blood pressure measurement revealed a 220/110mmHg value. In dynamics the laboratory tests showed thrombocytopenia and hepatocitolysis and an abdominal ultrasound exam was conducted and it showed a perihepatic hipoechoic image. Correlation of this data raised the suspicion for subcapsular hepatic hematoma associated with HELLP syndrome, this diagnosis being confirmed after a CT scan. The therapeutical management of the hematoma was to "watch and wait" and the HELLP syndrome`s was conservatory, with favorable results. Concluding, the association between subcapsular hepatic hematoma and HELLP syndrome and/or severe preeclampsia is a rare clinical finding yet it ought to be suspected in any eloquent clinical context, and carefully monitored by advanced imaging techniques.

Topic: 4.22 Postpartum management of high risk pregnancies

P229 Menstrual cycle pattern and pregnancy complications

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Context

Alterations of menstrual cycle are very frequent in female population, starting in adolescence and often continuing into adulthood. Most of these women will become pregnant during their life.

Objective

The aim of the study is to evaluate the maternal-fetal outcomes of the pregnancy of women with alterations in the menstrual cycle in adolescence and in adult life, focusing on their gynecological history as a potential risk factor for adverse pregnancy outcomes.

Methods

This is a prospective observational study. The primary objective is to evaluate the prevalence of the menstrual cycle alterations in adolescence and adult life. The secondary objective is the evaluation of the current evolution of pregnancy and the maternal-fetal outcome.

Patients

The patients (n. 400) were enrolled at first and second trimester of pregnancy at the first access to the high risk pregnancy clinic between November 2018 and May 2019. Women who gave birth at the Careggi University Hospital between March and September 2019 were evaluated. The inclusion criteria were: adult women, single pregnancy, Italian language speaking, known follow up at birth. Women with twin pregnancy, abortion, miscarriage or a late abortion were excluded.

Intevention

Data collection was performed by using a questionnaire that investigated the patient mother's clinical history, her pregnancy evolution and her first thousand days of life, including also the gynecological history since the menarche.

Results

The study group included 278 women. The mean age is 35.5 ± 5.2 and 22,7% of women were over 40 years. Nulliparous women were 70.3%. Women who reported heavy menstrual bleeding (HMB) in adolescence also had dysmenorrhea more frequently in youth (57.7% versus 25.9%, $p < 0.0001$); moreover, those who suffered from HMB in adolescence continued to have heavy cycles even in adulthood (37% versus 9.4%, $p < 0.0001$). Regarding the outcome of pregnancy, women with history of HMB in adolescence had a higher postpartum blood loss compared to women with normal bleeding ($p = 0.002$).

Conclusions

Women who had HMB in adolescence have a greater risk of postpartum hemorrhage. We could add HMB in adolescence to the already known risk factors of postpartum hemorrhage, helping us to predict and prevent it. The future objective is to expand the study sample with the aim of allowing women at risk of developing uterine disorders and thus complications during pregnancy and postpartum to be early identified.

Topic: 4.22 Postpartum management of high risk pregnancies

P230 Prevalence and risk factors of PPH in primigravida

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Introduction
According to WHO, postpartum haemorrhage is defined as blood loss of more than 500 mL following vaginal delivery or more than 1000 mL following caesarean delivery. Postpartum haemorrhage are still one of the leading causes of maternal deaths in Malaysia. All women who carry a pregnancy beyond 20 weeks' gestation are at risk for PPH and its sequelae. The risk factors of postpartum hemorrhage can be divided into three which are pre-pregnancy, antenatal and intrapartum.

Methods
We performed a case control study to identify the risk factors for post-partum hemorrhage among primigravida in Sungai Buloh Hospital from 2016 to 2018. From the calculation that we have done by using simple random sampling method, the required respondents are 75 for both case and control. The data collection method is an audit form. The data that we have obtained will be entered and cleaned using SPSS (a statistical software).

Results
From 2016 to 2018, we had identified 75 cases and 75 random controls of postpartum hemorrhage among primigravida. The risk factors associated with post-partum hemorrhage in primigravida that is significant with p value less than 0.05 are age (p=0.001), occupation which is self-employed (p=0.000), anemia during antenatal (p=0.000), uterine fibroid (p=0.007), method of delivery (p=0.000), total blood loss (p=0.000), prolonged labour >8H (p=0.005), instrumental delivery (p=0.006), extensive vaginal wall tear (p=0.009), cervical tear (p=0.013), 3rd or 4th degree tear (p=0.006), uterine atony (p=0.000) and vascular lower segment during caesarean section (p=0.029).

Conclusion
The results shows that the risk factors for post-partum hemorrhage in primigravida are age, occupation (self-employed), antenatal anemia, uterine fibroid, method of delivery, prolonged labour >8H, instrumental delivery, extensive vaginal wall tear, cervical tear, 3rd/4th degree tear, uterine atony and vascular lower segment during caesarean section.

Topic: 4.22 Postpartum management of high risk pregnancies

P231 Incidence and risk factors of postpartum haemorrhage in primigravida

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Introduction

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Methods

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Conclusion

The results showed that the risk factors for post-partum hemorrhage in primigravida were age, occupation (self-employed), antenatal anemia, uterine fibroid, method of delivery, prolonged labour more than 8 hours, instrumental delivery, extensive vaginal wall tear, cervical tear, 3rd/4th degree tear, uterine atony and vascular lower segment during caesarean section.

Topic: 5.3 Puberty and adolescent gynecology

P233 The prevalence of polycystic ovarian syndrome (PCOS) among secondary school students in Klang Valley, Malaysia

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Introduction
Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women, with prevalence ranging from 4-12%. There are no published reports of PCOS in adolescents in Malaysia. Hence, this study aimed to determine the prevalence of polycystic ovarian syndrome (PCOS) among secondary school students in Klang Valley, Malaysia.

Methodology
Female secondary school students in year 4 and 5 from three secondary schools in Klang Valley, Malaysia were recruited to join this study. Informed consents from their parents were obtained. They completed questionnaires on menstrual cycles and acne, as well as Ferriman-Gallwey charts and had pelvic ultrasound scans performed. PCOS was diagnosed based on their fulfilment of all three of Rotterdam Criteria: oligomenorrhoea, clinical hyperandrogenism (acne and hirsutism) and PCOS features on ultrasound scan.

Result
From 200 students, 170 (85.0%) completed all procedures and questionnaires. The mean age (SD) was 16.35 +/- 4.8 years. All had attained menarche, the majority had regular menses (127; 74.7%), with 11(6.5%) having oligomenorrhoea. The subjective assessment showed that 148 (87.1%) had acne, there were 28 (16.5%) with significant hirsutism and another 28 (16.5%) had sonographic evidence of PCOS. In total, there were 11 respondents (6.5%) who fulfilled the criteria for PCOS.

Conclusion
Thus, the prevalence of PCOS was 6.5%. Early diagnosis in adolescents enables early treatment and prevention of PCOS sequelae such as infertility, metabolic syndrome and endometrial pathology.

Topic: 5.3 Puberty and adolescent gynecology

P234 Clinical and laboratory features of different forms of endometriosis in adolescent girls

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Context

There are lack of data for early diagnosis of endometriosis in adolescence. It passes 7–10 years from the onset of the first symptoms to the final diagnosis.

Objective is to study the clinical and laboratory features of different forms of endometriosis in adolescent girls.

Methods

A case-control study was performed. In the main group 47 girls aged 13-17 years with a confirmed diagnosis of endometriosis on laparoscopy, without any malformations of the reproductive system were included. The control group consists of 30 healthy girls the same age.

Intervention

Groups of endometriosis patients and controls were compared by anamnestic, clinical, laboratory and instrumental parameters (CBC, endocrine, biochemical profile, ultrasound, MRI). Then the main group was divided, depending on the form of endometriosis: endometriosis externa (n=19), adenomyosis (n=16), endometrial cysts (n=11) and compared between subgroups and controls.

Results:

Compared to the group of healthy peers, patients with endometriosis were characterized by a heredity in endometriosis (38%, $p<0.001$), an earlier menarche (11.6 years, $p=0.037$) and heavy periods ($p=0.016$).

The main complaint of patients with endometriosis was pain in the first days (96%, $p<0,001$) and before menstruation (30%, $p=0.03$), arising on average 1.5 years ± 3 months after menarche, resistant to antispasmodics and NSAIDs, that should be considered in the diagnosis of endometriosis. Girls with adenomyosis were characterized with aggravated pregnancy of their mothers (threatened abortion, preeclampsia) (70%, $p=0.015$), according to anthropometry - a higher BMI compared to healthy adolescents (24.2 kg/m^2, $p=0.033$), which indicates relative hyperestrogenism in these patients.

Conclusions

Endometriosis should be suspected in girls with a set of the following clinical data: dysmenorrhea (pain on the eve and in the first days of menstruation, resistant to antispasmodics and NSAIDs), heavy menstruation, early menarche, increased BMI, aggravated pregnancy in mother and heredity of endometriosis in the immediate family. The most significant factors in the diagnosis of endometriosis in adolescents turned out to be an double increase in CA-125, the presence of endometrioid cysts according to ultrasound data (72.6% of the diagnostic accuracy), if external genital endometriosis is suspected – MRI of the pelvic organs (60% of the diagnostic accuracy according to MRI in comparison with 6.2% according to ultrasound, $p<0.001$).

Topic: 5.4 Female sexual function and dysfunction

P235 Optimization of the treatment of sexual dysfunction in women of reproductive age with androgen deficiency

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Objective

To improve the sexual health of women with androgen deficiency as a result of eliminating atrophic colpitis using plasma riched with growth factors.

Material and methods of research

Used by the algorithm for the evaluation and treatment of hypoactive sex drive disorder (HSDD). The study of the condition of the vaginal and vulvar mucosa was carried out two methods for diagnosing: vaginal pH, as well as counting the vaginal maturation index, analysis was performed on days 8-10 of the menstrual cycle. The patients underwent injection of PRGF plasma therapy 3 times with a difference of 3 weeks, after the last procedure, a repeated questioning of the patients was carried out.

Patients we examined 38 patients of reproductive age with sexual dysfunction in the presence of androgen deficiency. 2 groups were distinguished: the 1st group (20 people) of the patients receiving standard treatment and PRGP plasma therapy and the 2nd group (18) receiving only standard therapy.

The results and discussion

When comparing the indicators according to the HSDD an increase in the frequency of sexual contacts after therapy was noted by 80 ± 12% in patients of the 1st group and by 38 ± 13% in the 2nd group. Improving the quality of sexual life was noted by all patients (100%) of the 1st group and 47 ± 15% of the 2nd group. Satisfaction during sexual intercourse noted 67 ± 15% and 25 ± 8% of patients. The pH before treatment in the 1st group was 5.6 ± 0.7 and after treatment 3.8 ± 0.4, the pH in the 2nd group before therapy is 5.7 ± 0.8 and after treatment 4.9 ± 0.6. Before treatment: parabasal cells prevail, surface layer cells are absent in both groups. After treatment, surface cells prevailed in smears in the 1st group, and the karyopichesia index ranged from 30 to 50%. In the 2nd group intermediate cells predominate in smears in the presence of separate superficial and up to 10% parabasal cells.

Conclusions

treatment of sexual dysfunctions in women can include injection of PRGF plasma therapy, leads to the cure of atrophic colpitis ($p < 0.05$) and improvement of sexual health ($p < 0.05$).

Keywords: reproductive age, sexual dysfunction, plasma enriched with growth factors.

Topic: 5.4 Female sexual function and dysfunction

P237 A retrospective study of the association between sleep quality and female sexual function

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Context
Associations between sleep and sexual function in women have been previously described, but prior studies have not examined associations between sleep quality and sexual dysfunction as defined by sexual problems associated with personal distress.

Objective
To evaluate the associations of sleep quality and female sexual dysfunction (FSD) in sexually active women.

Methods
A cross-sectional analysis from the Data Registry on Experiences of Aging, Menopause and Sexuality (DREAMS) was performed based on questionnaires completed by women who presented to women's clinics at Mayo Clinic Rochester, Minnesota and Scottsdale, Arizona, between December 2016 and September 2019. DREAMS contains validated questionnaires including Female Sexual Function Index (FSFI), Female Sexual Distress Scale-Revised (FSDS-R), and the Pittsburgh Sleep Quality Index (PSQI) for assessment of sexual function and sleep quality, respectively. Associations between sleep quality and FSD were evaluated utilizing a multivariable logistic model adjusting for age, partner status, education, race/ethnicity, weight, reproductive status, depression, anxiety, and use of antidepressants and menopausal hormone therapy.

Participants
Sexually active women aged 40-65 years seen at Mayo Clinic women's health clinics during the study time frame who completed questionnaires and provided permission for use of their medical records for research.

Main outcome measures
Sleep quality (PSQI score ≥ 5, consistent with poor sleep quality) and FSD (FSFI ≤ 26.55 and FSDS-R ≥ 11).

Results
A total of 2,487 sexually active women were included in the analysis. Women were of mean age 53 years, partnered (88.1%), overweight (BMI mean 26.4, SD=5.7), educated (93.5% some college), employed (70.1%), white (91.5%) and postmenopausal (49.9%). Seventy five percent of women had poor sleep quality and 54% met criteria for FSD. On multivariable analysis accounting for multiple potential confounding factors, women with poor sleep quality were 1.48 times more likely to report distressing sexual problems (95% CI 1.21-1.80, $p<0.001$).

Conclusions
Poor sleep quality was associated with a greater risk for FSD. This study shows that in addition to its myriad other effects on health, poor sleep may be independently associated with FSD.

Topic: 5.4 Female sexual function and dysfunction

P238 Sexual dysfunction in reproductive-aged women with multiple sclerosis

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Objective
Despite a lot of studies of sexual dysfunction there are still no consistent data about the prevalence and characteristics of sexual dysfunction (SD) among women with multiple sclerosis (MS), especially it terms of disease severity and duration. The study aimed to determine the prevalence of various SD symptoms among female MS patients, depending on the age and severity of the disease, and evaluate SD impact on quality of life.

Methods
The study population included 116 female patients with MS (McDonald's criteria, 2010). Health - related quality of life was measured by the Multiple Sclerosis Quality of Life Questionnaire (MSQOL-54). Sexual dysfunction was assessed with the Sexual Function Index for Women with Multiple Sclerosis Questionnaire.

Results
A direct average correlation between satisfaction with sexual life and relationships; sexual activity and arousal; discomfort and pain during sexual intercourse; direct impact of multiple sclerosis on sexual life and total quality of life, physical health component, mental health component was established ($P < 0.05$). The prevalence of sexual dysfunction increases with the age and disease duration.

Conclusions
Our data confirm that SD significantly affect the quality of life in female MS patients. Every MS patient should be screened for sexual function disorders during routine counseling. Knowledge of the existence and prevalence of the problem, management options significantly increase the chances for patients seeking professional help.

Topic: 5.4 Female sexual function and dysfunction

P239 Female sexual function after different treatment regimens for Chinese patients with malignant tumors

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Objective

Presently sexual dysfunction does not get enough attention in patients with malignant tumors. Aim was to assess the status of Female Sexual Dysfunction (FSD) after treatment of malignant tumors of Chinese patients.

Methods

An online questionnaire according to the Chinese version of Female Sexual Function Index (FSFI) was given to 44 married patients with malignant tumors (tumor group) who got cryopreservation of their ovarian tissue at the first ovarian tissue cryopreservation bank in China (Beijing Obstetrics and Gynecology Hospital, Capital Medical University) from December 2018 to November 2019 and were compared with 33 women without tumors or other serious diseases (control group). For FSFI total score less than 26.55 the diagnosis of FSD was made.

Results

From 75 questionnaires received, 71 qualified questionnaires were evaluated anonymously, 38 from tumor group, 33 from control group. Mean age was 34 and 35 years ($p=0.078$), respectively. Median FSFI total score of tumor group (15.50) was significantly lower compared with control group (25.60) ($Z=-5.050$, $p<0.05$). 92.11% showed FSD in tumor and 42.42% in control group. The 38 malignant tumor patients can be divided into 3 groups: operation combined with radiotherapy or chemotherapy (n=28), simple operation (n=6) and non-operation group, only with radiotherapy or chemotherapy (n=4). Significant differences of FSFI for total score ($p=0.007$), scores of arousal ($p=0.008$), lubrication ($p=0.045$), orgasm ($p=0.097$), satisfaction ($p=0.004$) and pain ($p=0.007$) were found among the three groups. The FSFI total score and the scores of 6 dimensions in simple operation group were higher than those in operation combined radiotherapy or chemotherapy group.

Conclusions

Malignant tumor patients are at an increased risk of sexual dysfunction. Operation combined with radiotherapy or chemotherapy will cause a more serious effect on sexual function than operation alone. Therefore, more attention and treatment should be paid to the sexual function of patients after treatment for malignant tumors.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals'Ascent Plan, code: DFL20181401

Topic: 5.5 Sexually transmitted diseases

P240 Mathematical modeling for predicting genital tuberculosis in women

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Context
Tuberculosis of the female genitalia in most cases develops at reproductive age, does not manifest clinically or has nonspecific symptoms, leads to irreversible changes in the fallopian tubes and endometrium.

Objective
To develop a mathematical model for predicting genital tuberculosis in women from high risk group.

Methods
The logistic regression analysis included variables with the maximum correlation with the fact of genital tuberculosis in women and identified on the basis of the Spearman's rank correlation coefficient. The formula for calculating the likelihood of developing genital tuberculosis:
P=1/(1+e^(-z))
where P - is the probability of genital tuberculosis, e - is the base of the natural logarithm, z - is logit, which is defined as: z=b0+b1 x1+···bn xn, n=1-7
Logit coefficients take the following values: b0 = -0.111, b1 = -1.452, b2 = -0.186, b3 = 1.346, b4 = -1.443, b5 = -1.772, b6 = 3.185, b7 = 0.113, x1 = dyspareunia, x2 = algomenorrhea, x3 = subfebrile condition, x4 = hypo-oligomenorrhea, x5 = hyperpolymenorrhea, x6 = obstructed fallopian tubes according to the results of hysterosalpingography, x7 = test with the tuberculous recombinant allergen. The frequency of the true-negative and true-positive prognostic result, the sensitivity of the mathematical model were determined, ROC analysis was applied.

Intervention(s)
To assess the effectiveness of the model, we determined the Area Under Curve.

Patient(s)
We analyzed 129 women at risk for genital tuberculosis and 131 women treated for genital tuberculosis.

Main outcome measure(s)
The overall accuracy of the model was 81.5%, which is a quantitative assessment of the degree of coincidence of the model results with the real ones, p of the model = 0,000. The sensitivity for this model was 63.5%, the specificity was 90.5%. The value of AUC was 0.885, which indicates a high accuracy of predicting the results when using this mathematical model.

Result(s)
As a result of the analysis, factors were identified that significantly affect the prognosis of the development of female genital tuberculosis ($p < 0.05$): prolonged subfebrile condition of unclear etiology, obstructed fallopian tubes, a positive test with a recombinant tuberculosis allergen, and hypo-oligomenorrhea.

Conclusions
The developed mathematical model for predicting the development of genital tuberculosis, tested on 129 women, is adequate, has high specificity, and allows to identify patients among women at risk.

Topic: 5.6 Hormones and gynecological disorders

P242 Serum estradiol and CA-125 as a control in hormonal treatment containing only progestogen in women with pelvic endometriosis

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Objectives

To use serum estradiol and CA-125 control progestogen-only hormonal treatment in women with pelvic endometriosis.

Methods

One hundred and twenty seven patients diagnosed with pelvic endometriosis and treated for 12 months with 2 types of progestogen-only hormones were analyzed, 66 patients used tablets containing 75 mcg desogestrel daily orally (group 1) and 61 used dienogest 2 mg tablets daily orally (group 2), at Women's Health Reference Center (Hospital Perola Byington), São Paulo, Brazil. Evaluated for pain by visual analog scale (VAS), and they were followed with estradiol and CA-125 serum dosages at 0, 3, 6 and 12 months of treatment.

Results

Pain (VAS) results in the period of 0, 3, 6 and 12 months in group 1 were 9.1, 4.5, 2.3 and 2.7 mm, respectively; and group 2 were 9.2, 4.1, 3.3 and 3.6 mm, respectively. Estradiol dosages at time 0, 3, 6 and 12 months in group 1 were 83.4, 64.9, 54.3 and 70.2 pg / ml, respectively; and group 2 were 83.4, 64.9, 54.3 and 70.2 pg / ml, respectively. The dosages of CA-125 at times 0, 3, 6 and 12 months in group 1 were 45.1, 25.9, 23.3 and 19.6 U /, respectively; and in group 2 were 44.7, 29.7, 28.3 and 22.9 U / mL, respectively. There was a significant reduction in pain after 3 months of treatment in both hormones, as well as in CA-125 levels. Serum estradiol remained at high levels throughout treatment.

Conclusion

Clinical progestogen-only hormonal treatment in women with pelvic endometriosis and laboratorial follow-up with high serum estradiol dosage turned during treatment, despite good clinical response. Although, other studies must be directed to prove safety in long-term use of this medication.

Topic: 5.6 Hormones and gynecological disorders

P244 An atypical presentation of late onset congenital adrenal hyperplasia: a case report

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Context
The extent to which PCOS should be diagnosed in adolescence has been challenged. Hirsutism, oligomenorrhoea and multiple peripheral follicles on ultrasound clinically imply PCOS. However, this has been contested by the recent Monash guidelines. We present a case of hirsutism with an atypical presentation of CAH despite a clinical picture of PCOS.

Objective
To discuss the challenges associated with hirsutism, the PCOS guidelines and atypical late onset CAH.

Method
A Case report

Patient
A 18-year old female presented with hirsutism and oligomenorrhea for one year. She reached her menarche aged 13 and suffered with menorrhagia and irregular periods but reported no dysmenorrhoea. On examination, she had marked hirsutism affecting primarily her neck and prominent side burns. She had a raised DHEA-S of 17.1umol/L but her hormonal profile was otherwise unremarkable. The role of DHEA-S in determining PCOS is unclear but those with CAH demonstrate that DHEA-S excess can result in a PCOS-phenotype. Ultrasound revealed bilateral prominent ovarian size with small peripheral follicles, which may indicate PCOS. However, under the Monash 2018 guidelines, ultrasound should not be used to diagnose PCOS in patients <8 years post menarche. This is due to the high incidence of multi-follicular ovaries in this life stage. Moreover, although investigating serum testosterone is recommended, DHEA-S is not.

Intervention
The patient took an oral contraceptive to relieve her symptoms but her DHEA-S remained increased. An adrenal CT scan was normal.

Main Outcome
In view of her androgen profile, the diagnosis of PCOS based on clinical hyperandrogenism and oligomenorrhoea was less likely and thought to be an adrenal enzymatic deficiency.

Result
Most CAH presentations are caused by a 21-hydroxlase deficiency resulting in elevated 17-OHP levels. However, our patient had a normal 17-OHP but an increased DHEA-S level and so a 3-beta-hydroxysteroid dehydrogenase deficiency was more likely.

Conclusion
Although adolescent hirsutism is most commonly associated with PCOS, we should also consider diagnoses such as non-classical late onset CAH. The recent Monash guidelines limit a diagnosis of PCOS with positive ultrasound findings less than 8 years post menarche and state that measuring DHEA-S is of limited value. However, finding a raised DHEA-S and normal testosterone/androstenedione profile can points towards a 3-beta-hydroxysteroid dehydrogenase deficiency.

Topic: 5.6 Hormones and gynecological disorders

P245 Assessment of the *in vitro* short time bactericidal activity of two local treatments against bacteria involved in vaginosis

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Context

Bacterial vaginosis is the most prevalent cause of abnormal vaginal discharge in women. It is characterized by an overgrowth of anaerobic organisms in the vagina leading to a replacement of lactobacilli and an increase in vaginal pH.

Objective

To compare the kinetic of bactericidal activity of two marketed local treatments against four common anaerobic/microaerophilic microorganisms involved in bacterial vaginosis.

Methods

Products tested: Neomycin-Polymyxin B-Nystatin (NPN) and Metronidazole marketed formulation (reference).
Dilutions: 1/2, 1/4, 1/8, 1/16, 1/32, 1/64 and 1/128 (V/V).
Strains: Prevotella bivia (Gram -), Gardnerella vaginalis (Gram +), Atopobium vaginae (Gram +), Mobiluncus curtisii (Gram -).
The bactericidal activity of each product on the four strains was assessed by dilution-neutralization method according to product dilutions and to the contact time, i.e. 1h and 4h. Assays were performed with or without serum to explore potential interferences. The higher log reduction, the more efficient product/dilution tested.

Results

Prevotella bivia:
For Metronidazole, the log reduction for all tested dilutions was very low after 1h contact while NPN combination maintained a high log reduction for all the tested dilutions after 1h and 4h contact with or without serum.
Gardnerella vaginalis:
For Metronidazole, no effective bactericidal activity was observed at all tested dilutions after 1h contact while NPN combination demonstrated a concentration dependent log reduction. After 4h contact, a slight increase of log reduction was observed for Metronidazole, while NPN combination showed high log reduction even in the presence of serum.
Atopobium vaginae:
For Metronidazole, no effective bactericidal activity was observed at all tested dilutions after 1h and 4h with/without serum while NPN combination indicated a concentration dependent effect with lower bactericidal activities in the presence of serum.
Mobiluncus curtisii:
For Metronidazole, no effective bactericidal activity was observed at all tested dilutions after 1h and 4h with/without serum while high log reductions were maintained at all tested dilutions for NPN combination with concentration dependent bactericidal activity in the presence of serum.

Conclusion

The combination Neomycin-Polymyxin B-Nystatin has a faster bactericidal action on the four tested bacteria considered involved in bacterial vaginosis, in comparison with the reference treatment Metronidazole.

Topic: 5.6 Hormones and gynecological disorders

P246 The relevance of sense of coherence to premenstrual syndrome and depression state of young women in Japan

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Context
There are not few young women who have a problem of Premenstrual Syndrome (PMS), and depression relevant to this problem. These days, Sense of Coherence (SOC) which is self-stress coping ability attracts attention, and high SOC is thought that there is a tendency to catch stresses positively. We predicted that women with high SOC have low PMS and depression state.

Objective
The purpose of this study is to clarify the relevance of SOC to PMS and depression state of young women in Japan.

Methods
We conducted a questionnaire survey for 79 Japanese young women.

Participants
All subjects were university students, 21.2±1.9 years old, and 28.7±4.2 days of menstrual cycle.

Main outcome measures
Stress coping ability was measured with the Sense of Coherence (SOC-13) scale (Antonovsky, 1987; trans Yamazaki etc., 2001) (α=.82). The Premenstrual Dysphoric Disorder scale (Miyaoka etc., 2009) was used for evaluation of the condition before menses. The Japanese version of Self-Rating Depression scale (SDS, Fukuda etc., 1973) was used for evaluation of a depression state (α=.81).

Results
The number of participants with PMS was 15 (19.0%). The average value of SOC was 59.4 (±10.1), the median was 60.0. Since we divided into two groups at the median of SOC, the number of High group was 39 (≥ 61) and Low group was 40 (≤60). As a result of correlation analysis of SOC and SDS, a significant negative correlation was found (r=-.62 p =0.000). As a result of chi-squared test, a significant difference was detected between the High and Low groups of SOC in the existence of PMS condition (p=0.002). In terms of the SOC score, a significant difference was observed between the group without PMS (n=64, 60.6±10.7) and with PMS (n=15, 54.7±5.0, p=0.003).

Conclusions
The relevance of SOC to PMS and SDS was evaluated in this study. SOC is an individual capability of coping with stresses, and it is formed at adulthood through all kinds of experiences from childhood. Therefore, even if it is the same condition of PMS, reaction for the condition may change with individual SOC levels.

Topic: 5.6 Hormones and gynecological disorders

P247 Aspects of hormonal disorders by patological uterine bleeding among women of reproductive age with cronic viral hepatic lesion

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The problem of viral hepatitis and menstrual dysfunctions stays present, being determined by the high incidence and severity of physiopathological abnormalities, specific to these associations. In Republic of Moldova 9% of population are chronic carriers of HVB, HVC affects 1.5-5% of population.

Objectives

To study pathogenic aspects of appearance of dysfunctional uterine bleeding in women with chronic viral hepatitis.

Materials and methods

According to the objective there have been processed the results of examination of 160 patients. Inclusion criteria: age between 18-40 years, irregular menstrual cycle, and absence of pelvic pathological organs as well as related endocrine disorder. The hormonal profile has been evaluated using IEA (estradiol, progesterone, FSH, LH, prolactin).

Results

Patients average age - 26.0 ± 5 years. Regular menstrual cycle was present only in 7.5 ± 2.48%. Hypermenstrual syndrome and uterine bleeding were found in 72 patients (methrorrhagia 27±1,3% and menorrhagia 17,86±1,45%). 22.6 ± 1.48% patients revealed a hypomenstrual syndrome. The disorder was more manifest in patients with chronic C hepatitis (35,3±2,3%) and in those with mixed forms of hepatitis (28,58±1,08%). Analysis of hormone profile reflects a wide range of variations in the content of estradiol (from 70.3 to 670 nmol / l) and progesterone (from 1.42 to 5.5 nmol / l). Hyperestrogenemia prevail in patients with severe VHB and those with mixed forms (in 63.75 ± 3.1% cases). Progesterone plasmatic concentration was dropped in 67,5±2,9% patients and varied from 1,42 to 7,42 nmol/l, thus indicating an essential hypoprogesteronemia ($p>0,05$), FSH seric concentrations (6,62±0,3 mME/ml) and LH (2,7±0,08 mME/ml) slightly exceeded the maximal tolerated limit. High levels of Prolactin were registered (505,3 ± 46,3 ng/ml ($p<0,05$)) in the majority of cases.

Conclusions

The results of the study reveal serious disturbances in all hepatic functions in patients with viral hepatitis with direct repercussions over the ovaries, which lead to derangements in ovarian hormone biosynthesis. Hyperestrogenemia is the main factor that changes the menstrual cycle rhytmicity and duration, which result to uterine bleeding manifested by methrorrhagia and menorrhagia.

Topic: 5.6 Hormones and gynecological disorders

P248 Investigating pathogenesis of endometriosis with AG-205, an alleged PGRMC1 inhibitor

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Context and objective

It has been suggested that Progesterone Receptor Membrane Component-1 (PGRMC1) is involved in gynecological pathologies. A conditional PGRMC1 KO in the mouse female reproductive tract induced subfertility and spontaneous development of endometrial cysts [McCallum ML et al., 2016]. Decreased PGRMC1 expression was observed in the stroma of human endometriosis lesions [Bunch et al., 2013 & our unpublished data]. Moreover, PGRMC1 was identified as a new regulator of TNF-α-induced matrix metalloproteinase (MMP)-9 activity in trophoblastic cells [Allen TK et al., 2014]. MMPs are suspected to favor the pathogenesis of endometriosis.

The purpose of this study was to use AG-205, an alleged "specific inhibitor of PGRMC1" (according to publications and commercial sources) to investigate the potential roles of PGRMC1 in the pathogenesis of endometriosis with a special interest for extracellular matrix (ECM) remodeling and/or hormonal regulation.

Methods

AG-205 was added in cultures of a human cell line derived from immortalized endometrial fibroblasts (T-HESC). In parallel, PGRMC1 expression was down-regulated in the same cell line via siRNA transfection. The impact on gene expression, by comparison with appropriate controls (DMSO or siRNA-control), was evaluated by whole transcriptome RNA sequencing (RNAseq) and by RT-qPCR for specific genes.

Results

In T-HESC cultures, we found that AG-205 induced expression of MMP-1 and MMP-3, and modified the expression of various enzymes involved in cholesterol synthesis and steroidogenesis. Effects of AG-205 identified by RNAseq were confirmed by RT-qPCR for specific genes. However, data from both RNAseq analyses (AG-205 vs siRNA) differed strikingly. The specificity of our siRNA for PGRMC1 was checked and results were confirmed with another siRNA. Our data support recent publications stating that PGRMC1 is not the (unique) target of AG-205.

Conclusion

In immortalized endometrial fibroblasts, AG-205 increases MMP-1 and MMP-3 expression and could be a potential modulator of estrogen (and progesterone) local metabolism (intracrinology), but independently of PGRMC1.

Topic: 5.6 Hormones and gynecological disorders

P248b Features of reproductive hormonal profile of servicewomen in the current war environment

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Introduction

According to our previous studies, servicewomen in the conditions of the military environment are more receptive to war zone stress-factors than their male colleagues and are more inclined to the development of unconscious psychosomatic problems associated with impaired reproductive health.

The aim

Evaluation of the functional state of the reproductive system according to hormonal studies in servicewomen in the zone of armed conflict.

Materials and methods

The study included 66 military women who had the gynecological complaints, whose reproductive hormonal profile for their blood content has been evaluated for: estradiol, testosterone, progesterone, prolactin, and cortisol. The evaluation was held directly during their stay in the military operation area.

Results

According to the results of research, statistically significant higher levels of progesterone and prolactin were determined in the military women (U = 17,0 p = 0,001) and (U = 44,0 p = 0,009) compared to levels for civilian women: 8,95 (6,70-14,38) i 4,25 (3,15-5,20) nmol/l for progesterone and 12,10 (8,48-17,23)-7,75 (6,13-9,63) ng/ml for prolactin. The increased levels of progesterone in the first phase of the menstrual cycle were captured in female soldiers in 70,0±20,6% of cases that might testify to the adrenal genesis of hyperprogesteroneemia and reiterate the stress-associated nature of hormonal disorders in this category of patients.

Conclusions

The revealed hormonal changes can play a significant role in the development of menstrual and reproductive function disorders for military women who are or have returned from the zone of armed conflict. This well-defined problem requires following deepened research.

Topic: 5.6 Hormones and gynecological disorders

P249 Menstrual cycle and quality of life: the Global Menstrual Distress Score (GMDS)

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Objective

The objective of the study is to define whether the menstrual cycle, in women without a diagnosis of gynecological pathology, can be related to psychopathological, relational and psychological disorders, also based on the use of oral contraceptives, delivery, age, psychiatric disease, the abundance of menstrual flow, the regularity of the cycle.

Methods

The study evaluated 105 women of childbearing age, without gynaecological pathology, recruited at the Department of Integrated Maternal and Childhood Activities (DAIMI) and at the SOD complex (SODc) of Psychiatry of the University Hospital of Careggi. Patients responded to a questionnaire on the perception of cycle-related stress containing 25 items, on the basis of which the GLOBAL MENSTRUAL DISTRESS SCORE (GMDS) was calculated, which evaluates the overall stress related to the patient's menstrual cycle; the MESI (MEnses Specificity Index), which represents the proportion of symptoms reported by the patient present only in the days of menstruation; the intermediate scores for each item. The statistical analyses were carried out with IBM SPSS Statistics Version 23 software using chi-square tests, the Fisher's exact test, the Mann-Whitney test, depending on the type of variable studied.

Results

There are no significant differences in terms of GMDS and MESI in relation to contraceptive therapy use, delivery, age and cycle regularity. However, the prevalence of some cycle related symptoms, varies depending on equality, age, presence of psychiatric disease, abundance of flow. Significant differences were also observed in the percentage of symptoms associated with the cycle measured by MESI in relation to the presence of psychiatric disease, but not in the overall stress measured by GMDS. Finally, women with abundant menstrual flow presented an increase in GMDS but not in MESI.

Conclusions

The GMDS is a valid method to calculate stress associated with the menstrual cycle in healthy women, regardless of the use of contraceptive therapy, age and in parous or nulliparous women. Women with an abundant menstrual flow have a higher stress related to the menstrual cycle. In addition, those with a history of psychiatric pathology have higher percentage of symptoms associated with the cycle. The use of this tool can be a valid method of quantification of stress related to the menstrual cycle, with the potential to be administered in case of uterine disorders, in the evaluation of the response to therapies.

Topic: 5.7 Endometrial regulation

P250 Endometrial receptivity characteristics in women with different functional activity of ovarian corpus luteum

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Objective
To study the endometrial expression of estrogen (ER) and progesterone (PR) receptors in cases of different functional activity of ovarian corpus luteum (serum progesterone (P) level: (low) 16.1≤P<30 nmol/l and (high) P≥30 nmol/l functional activity) in women with a history of reproductive dysfunctions.

Materials and methods
There were main (I) (121 patients with infertility (n=81) and miscarriages (n=40) in the anamnesis) and control (II) groups (16 healthy fertile women) (age 20-40 years old). We performed endometrial biopsy and obtained peripheral blood on 6-8th day after ovulation. We conducted histological and immunohistochemical (ER, PR expression) analysis of endometrium samples.

Results
Women of the both groups had ovulatory menstrual cycle (P≥16.1 nmol/l); the serum estradiol (E2) level (pmol/l) was 692.2±29.1 (I) vs 707.4±66.1 (II); P (nmol/l) – 45.1±2.0 (I) vs 39.1±4.9 (II) (p>0,05 for all cases). Mid-secretory endomeirum was determined in healthy women and in 42% (n=51) in the main group. All healthy women and 44% (n=53) of II group showed low glandular ER, PR expression, reduced stromal ER expression, high PR stromal expression in endometrium.
In the cohort of women with normal hormone-receptor endometrial interactions (n=69) (n=16 in I and n=53 in II) serum P<30 nmol/l was found in 36% (n=25) of cases, P≥30 nmol/l – in 64% (n=44). In this cohort H-score count of ER, PR had no differences in cases with high (1) or low (2) functional activity of ovarian corpus luteum: ER in glands 106,8±7,6 (1) vs 109,2±5,9 (2), ER in stroma 111,1±9,5 (1) vs 100,8±13,3 (2), PR in glands 28,5±4,4 (1) vs 30,4±5,9 (2), PR in stroma 266,1±6,5 (1) vs 278,0±3,3 (2) (p>0,05 for all cases).
In 56% (n=68) of the women of the main group with disturbed endometrial 'response' low functional activity of ovarian corpus luteum was observed in 25% (n=17), high – in 75% (n=51) of cases. No significant differences were found in ER, PR H-score count in dependence of high (1) or low (2) functional activity of ovarian corpus luteum: ER in glands 204,2±10,7 (1) vs 236,1±16,7 (2), ER in stroma 174,0±11,7 (1) vs 157,2±21,8 (2), PR in glands 239,0±9,2 (1) and 231,7±22,7 (2), PR in stroma 271,6±3,8 (1) vs 271,1±7,5 (2) (p>0,05 for all cases).

Conclusions
In women with ovulatory menstrual cycle the higher serum P level was not determined as a factor correlating with higher frequency of normal hormone-receptor interactions in the endometrium.

Topic: 5.7 Endometrial regulation

P251 Cdk2ap1 regulates proliferation and decidual differentiation of mouse stromal cells during implantation

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Context
Stromal preparation for implantation is defined by the differentiation for decidua formation. It regulates and maintain embryo development. For such a differentiation, the proliferation of endometrial stromal cell should be controlled through steroid hormones. However, the cell proliferation control is not well evaluated at this period. In mice, decidual reaction starts in 5 day of gestation, and stromal cells adjacent to the embryo form the primary decidual zone (PDZ) and the outer cells to proliferate continuously, to form a secondary decidual zone. Cdk2ap1 is known as growth suppressor identified and isolated from normal keratinocytes. Our previous study demonstrated that Cdk2ap1 mRNA is mainly localized to proliferating tissues.

Objective
To evaluate the role of Cdk2ap1 during decidualization, we profiled the Cdk2ap1 protein expression and localization and examined the functional roles of Cdk2ap1 during implantation.

Methods
Real-time PCR technology, Western blotting, immunofluorescence method and *in vitro* decidualization-induction with transfect technology were employed.
Experimental Animals
6-8 weeks old female CD-1 (ICR) mice were used

Intervention(s)
CD-1 females were mated with fertile males of the same strain to induce pregnancy and were checked for vaginal plugs on the following morning. The day on which the vaginal plug was noted was considered as day 1 of pregnancy. The mice were sacrificed to collect uteri on day 1, 2, 3, 4, 5, 6, 7, 9 and 12 of gestation. Pregnancy on day 1–12 was confirmed by recovering embryos from the reproductive tracts at from 10:00 to 11:00 AM. The embryos were removed from oviducts or uteri by flushing with DEPC-treated PBS (PBS).

Main outcome measure(s)
Cdk2ap1 expression level was measured with qRT-PCR, Western blotting, and immunofluorochemistry. In addition, Cdk2ap1 expression was knockdown and overexpression.

Results
At the time of implantation, Cdk2ap1 protein level was significantly increased. Cdk2ap1 was localized in the stromal cell. Cdk2ap1 knock-down suppressed decidual events but Cdk2ap1 overexpression accelerated decidualization.

Conclusion
These results show that Cdk2ap1 regulate the stromal cells proliferation on the pregnant stage dependently and differentiation of endometrial cells during implantation.

Key words: decidualization, implantation, Cdk2ap1, proliferatiom

Topic: 5.7 Endometrial regulation

P252 Endometrial dystrophy is a visual, histological, cytogenetic diagnosis

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Context

Dystrophy is a qualitative change in the chemical composition, physico-chemical properties and morphology of cells and body tissues associated with metabolic disorders. Endometrial dystrophy hysteroscopically is a structureless, fibrous tissue against a background of normal endometrium, looks like an algae. Pathologically dystrophy is characterized by the presence of parts of the endometrium in the secretory phase against the background of the endometrium in a proliferative phase
Endometrium in patients with dystrophy characterized by cytogenetic instability.

Objective

Make a diagnosis of endometrial dystrophy. Develop the algorithm of management of patients with endometrial dystrophy.

Methods

The study group included 22 women, aged 28 to 46 years old, with infertility and IVF failures in their medical histories. All patients underwent hysteroscopy and endometrial biopsy followed by a histopathological study of endometrial samples stained hematoxylin-eosin. Cultivation of endometrial phase cells proliferation and karyotyping of metaphase chromosome preparations (GTG - staining) was performed.

Results

The number of patients with primary infertility was 6 (32%), with secondary infertility - 16 (68%). IVF history of failure in 21 patients. All patients underwent hysteroscopy with partial resection and endometrial biopsy. Dystrophic endometrial changes were detected in 20 patients (91%). Karyotyping endometrium showed aneuploidy count of more than 5% in 100% of cases. After partial resection of the endometrium and hormone replacement therapy the pregnancyhas come in 6 patients (27%).

Conclusion

Endometrial dystrophy is the cause of infertility and is accompanied by IVF failures. Cytogenetically dystrophic altered endometrium occurs by instability of the chromosome apparatus of its cells. Treatment aimed at improving the structure and endometrial thickness, gives positive results. Endometrial dystrophy requires further research to determine the algorithm of identification and management of patients with this diagnosis.

Topic: 5.7 Endometrial regulation

P253 Chronic follicular endometritis is a clinico-pathologic form of chronic endometritis with an unfavorable clinical behavior

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Context

High percentage of unsuccessful IVF and recurrent miscarriage rates determinates a rationale of morphogenesis, on-time diagnostics and pathogenetically targeted therapy of chronic endometritis

Material and methods

The endometrium biopsy was taken in 964 women with history of infertility and after ineffective attempts of IVF and investigated by histological methods.

Results

Two clinico-pathologic forms of chronic endometritis (CE) were described: polypoid (PCE) (27.4 % (264)) and follicular (FCE) (14.9% (144)). PCE is characterized by villous and papillary vegetation on endometrial surface epithelium, micropolyposis is developing with formation of villous and papillary-like papillomatosis less 1mm. FCE is a form of chronic endometritis with formed of lymphoid-like follicles. Both forms of CE are often a background for polyps, intrauterine adhesions and «thin endometrium».
After the treatment 31 patients (of 144) with FCE and 235 (of 264) with PCE were included into the IVF protocol. Pregnancy was diagnosed in 15 of 31 women with FCE, 7 of 15 was diagnosed with missed abortion. In a PCE-group pregnancy diagnosed in 114 (of 235) women and 1 (of 14) was diagnosed with missed abortion. FCE is a clinico-pathological type of CE with unfavorable clinical behavior and the risk of unsuccessful IVF is 5,8 times higher (RR= 5,8; 95% CI 1,8-15,1) in comparison with PCE (p=0,0004).

Conclusion

FCE is a clinico-pathologic form of chronic endometritis with an unfavorable prognosis of the clinical course. A new approach to histological diagnosis of two clinic-pathologic forms opens up prospects for reproductologists to develop individual targeted therapy of chronic endometritis and prevention of IVF failure.

Topic: 5.9 Pelvic pain

P255 Burkitt lymphoma in an adult AIDS C2 female patient

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Introduction

Burkitt lymphoma is a high-grade B-cell lymphoma classified as a non-Hodkin lymphoma. Immunodeficiency-associated Burkitt lymphoma is usually associated with HIV infection or occurs in post-transplant patients taking immunosuppresive drugs.

Case report

We report the case of a 24- year-old female patient with stage C2 HIV infection presenting with complaints of fatigue and altered general status. She reported having amenorrhea for 4 months and pelvic pain. Her medical history was characteristic to lack of compliance with treatment, the viral load remaining high despite the prescribed intensive antiretroviral treatment. Intraoperatively we found: hypoplastic uterus of 30/20/20 mm in size and complete cystic transformation of the right ovary, the cyst size being of about 60/50 mm and the capsule intact. A right adnexectomy was performed. Immunohistological assessment about one month after surgery made the final diagnosis of Burkitt lymphoma. Studies show that an old HIV infection is associated with a higher risk for non-Hodgkin lymphoma (NHL) compared to patients with quite recent HIV infection.

Conclusions

The reported case had high CD4 levels at the time of diagnosis and also a particular extranodal involvement, the right adnexa. The CD4 level was 198/mmc at the time the adnexal tumor was discovered, level reached after a long period of time of low CD4 levels and high viral load.

Topic: 5.9 Pelvic pain

P256 An extra pulmonary tuberculosis patient, abdominal tuberculosis with pseudo-meigs syndrome mimicking an advanced ovarian cancer case report: rare case

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Background

Tuberculosis (TB) is still major worldwide concern. It is estimated that between 10-25% of TB infections occur extra pulmonary. Abdominal Tuberculosis occurs about 10 % of extra pulmonary tuberculosis. Pseudo Meigs syndrome is co existence of pelvic tumour, hydrothorax, and ascites resembling with metastatic ovarian cancer. Abdominal tuberculosis may resemble with advanced ovarian cancer.

Case Report

A married woman, 21 years old, with chief complaint enlargement stomach since 2 weeks, poor intake, low-grade fever, pelvic pain. Her father was diagnosed tuberculosis. Ascites was presented. Thorax X ray found right effusion plural. Peritoneal Fluid Analysis found LDH 905 U/L, PMN count 1050/ uL, MN count 3829/ uL, Glucose 68 mg/dL, Protein 7.2 g/dL, SAAG 0.8 mg/dl. ADA test from effusion pleural 4,44 U/L.CA-125 level (542.5 U/mL). Contrast MSCT abdominal found septal cyctic lesion suspected malignant ovarian mass. Laparotomy found serous ascites, multiple nodules attached to the surface of uterus and bilateral ovary, dense adhesions between uterus and rectum. Histopathology found Datia Langhans with necrotizing granulomatous changes with no malignant cells. Acid fast stain tuberculosis was positive at paraffin block pathology. After 2 months treatment antituberculosis, patient feel better and still on treatment.

Discussion

The patient presented ascites, pleural effusion, cystic ovarian suggestive of Pseudo-Meigs syndrome. CA-125 is elevated 80% of post menopausal ovarian cancer but not specific and non diagnostic in premenopausal women. SAAG < 1.1 mg / dl indicates non Portal hypertension. Datia Langhans at histopathology could be considered as tuberculosis but it can be revealed from another disease. Acid fast stain positive increase the probability of tuberculosis infection. Family history of tuberculosis infection could increase diagnostics value of tuberculosis. Antituberculosis according to the latest protocol led to clinical improvement.

Conclusion

Extra Pulmonary Tuberculosis (TB) should be being considered in the differential diagnosis of advanced ovarian cancer, especially in the regions that are endemic for the disease.

Keywords: pseudo meig syndrome, abdominal tuberculosis, tuberculosis, ovarian cancer

Topic: 5.9 Pelvic pain

P257 Cervical endometriosis presenting as a cervical mass causing hypogastric pain, obstructive uropathy with vaginal septum: a case report

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Cervical endometriosis is uncommon with prevalence of 2.4% and is usually an incidental or retrospective finding on histopathology. Endometriosis is defined as the presence of endometrial-like tissue outside the uterus resulting in a chronic, inflammatory reaction leading to microscopic bleeding, development of painful endometriomas, inflammation, fibrotic scarring and formation of adhesions. Depending on location, it presents with varied symptoms from pelvic pain, infertility, dyspareunia, and obstruction.
Presented is a case of a 34 year old, nulligravid who initially presented as pelvic pain with cervical mass causing obstructive uropathy.
Eight years prior, reported gradual decrease in quantity of menses, occurring irregularly lightly soaking 1-2 pads. No other symptoms. One year prior, noted cessation of menses and intermittent hypogastric pain, 2/10, crampy, nonradiating. Four months prior to admission, reported severe generalized abdominal pain 8/10 crampy with associated difficulty of voiding prompting consult.
On speculum exam, vagina smooth, noted 0.2 cm opening at 9 o'clock position of a blind pouch. Cervix was not visualized.
Internal examination, normal genitalia and smooth vagina about 3 cm in length ending in a blind pouch with minimal bleeding. Corpus is small. Rectovaginal exam revealed solid, palpable non-movable mass at the cul-de-sac measuring 4x5 cm.
After laboratory and work-up, revealed endometriosis. But due to the recurrent pelvic pain not relieved by medical treatment and not desirous of pregnancy, patient opted for removal mass and proceeded with laparotomy, adhesiolysis, total hysterectomy with bilateral salpingectomy, bladder insufflation, diagnostic cystourethroscopy. Final histopathology revealed cervical endometriosis; leiomyoma uteri; chronic salpingitis.
Endometriosis is a persistent disease affecting women of reproductive age. Classic symptoms are pelvic pain, dysmenorrhea, dyspareunia, and infertility. A thorough combination of history, physical examination, laboratory and additional diagnostic studies as indicated can determine the cause of pelvic pain and rule out other non-endometriosis concerns. Expectant management would be appropriate in asymptomatic patient. However, surgical management should be reserved for patients with persistent symptoms who are not desirous of pregnancy. The rarity of cervical endometriosis and this patient's case is interesting in that its pathology explains the symptomatology of patient.

Topic: 5.9 Pelvic pain

P258 The specificity of chronic pelvic pain in women with deep infiltrating endometriosis and infertility

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Context

The genesis of chronic pelvic pain (CPP) in women with deep infiltrating endometriosis (DIE) is caused not only by inflammation, pelvic adhesive disease, nerve damage, but also by neoneurogenesis and involvement of the central nervous system in the pathological process with the formation of «central sensitization».

Objective

Identify innervation features in the focus of endometriosis in women with chronic pelvic pain and infertility.

Methods

In assessing the structure of pain was taken into account the nature of the pain, which was determined in accordance with Visual Analogue Scale (VAS), to organize the symptoms of neuropathic pain and analyze their intensity rating scale was used Pain Detect.

Patient(s)

The study were examined 30 patients with DIE. The criteria for inclusion: age from 18 to 40 years; genital endometriosis confirmed with laparoscopy; the presence of pain lasting longer than 6 months; menstrual function. Exclusion criteria: uterine fibroids; varicose veins; inflammatory diseases of the pelvic organs; receiving hormonal therapy within the previous 6 months of the study.

Intervention(s)

The preparation of a focus of endometriosis for immunohistochemical study was performed during operative laparoscopy. Evaluated the expression of PGP 9.5 in immunohistochemical examination. The optical density and the relative expression area of the PGP 9.5 were evaluated.

Main outcome measure(s)

Expression of PGP 9.5 increases with worsening pain. This testifies to the fact that the basis for the formation of neuropathic pain is neoneurogenesis.

Result(s)

A significant direct correlation was established between the average expression area of the neuronal marker PGP 9.5 and pain intensity according with VAS ($R = 0.7$; $p < 0.05$) and Pain Detect scale ($R = 0.59$; $p < 0.05$). Infertility occurred in 11 out of 30 patients (36.7%) among patients with DIE and CPP. The expression of the neuronal marker PGP 9.5 in the tissues of endometrioid infiltrate in patients with CPP and infertility was significantly lower than in fertile patients (22.23 ± 17.41 and 10.73 ± 14.34).

Conclusions

The lower values in DIE of the neuronal marker PGP 9.5 in patients with infertility are due to the fact that the dominant infertility in such patients inhibits the development of afferent connections, and accordingly, prevents the aggravation of pain.

Topic: 5.9 Pelvic pain

P260 Histological and immunohistochemical features of ectopic foci in women with painful course of external genital endometriosis

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Introduction

Endometriosis is a chronic gynecological inflammatory disease in which dysregulation of the immune system plays a role in its initiation and progression. Due to the altered concentration of sex steroid receptors and other signaling defects, the eutopic endometrium is characterized by progesterone resistance, which is the cause of heterotopy invasion and increase in their number. Numerous studies are conducted worldwide to determine the pathogenetic mechanisms of endometriosis, but its etiology is still unknown.

The most complex and frequent complication of endometriosis from the standpoint of understanding the pathogenesis is chronic pelvic pain syndrome (CPPS). Its formation is based on macrophage dysregulation and "de novo" innervation in ectopic foci. It is known that endometriosis is an estrogen-dependent disease, and local hyperestrogenism leads to increased secretion of chemokines from nerve terminals, increasing the number and changing the polarization of macrophages in endometrioid tissue. Macrophages play an important role in the expression of multiple nerve growth factors (NGF), and under the influence of estrogen, the coexistence of macrophages and nerves forms a so-called neuromuscular bond that leads to the sensitization of peripheral nerves, forming a neuropathic component of pain in endometriosis.

Thus, endometriosis, being one of the most mysterious, complex and still completely incurable diseases, is by nature built on the mechanisms of immune imbalance. Immunological theory of EGE origin considers the formation of heterotopias as a result of inflammation, peritoneal irritation by products of retrograde menstruation, exposure to infections (especially viral), the use of corticosteroids, immunosuppressants, ionizing radiation, the influence of other environmental factors, as well as genetic conditioning. Undoubtedly, the formation of local productive inflammation is a triggering mechanism not only for the progression of the disease, but also for the development of complications, such as chronic pelvic pain syndrome, which eventually acquires automation and centralization.

However, to date, there is insufficient evidence in favor of a direct relationship between the area of lesion of EGE, the features of macrophage activity in ectopic foci and the degree of severity of pain syndrome.

Given the urgency of the above problem, we conducted a study aimed at determining the features of local inflammation in the foci of endometriosis in women with CPPS and the relationship of these parameters with the duration of pain syndrome.

Materials and methods

The study included 135 patients of reproductive age with stage III-IV NGE (revised classification R-AFS, 1996). Women were divided into 2 groups: group I (105 people) – with EGE and CPPS, group II (30 people) - with pain-free course of EGE. All patients underwent laparoscopy with visual assessment of ectopic foci and their subsequent excision in order to diagnose and treat EGE. The obtained material was subjected to histological and immunohistochemical (IHC) studies. On histological preparations of EGE with the presence of lymphoid infiltration, an additional IHC study was performed on lymphocyte antigens: expression to t - and B-lymphocyte antibodies was determined by indirect IHC method using secondary antibodies labeled with peroxidase.

Results

During laparoscopy, it was noted that macroscopically ectopic lesions looked like areas of brownish-bluish, red or white color. Foci with brownish-bluish color according to the results of histological conclusion contained the maximum number of hemosiderophages and free hemosiderin.

In endometriotic implants red color was detected in fresh and altered erythrocytes, hemosiderin and free hemosiderin in small quantities. White ectopias were deformed endometrial glands with perifocal sclerosis and the presence of single hemosiderophages. In this regard, it can be assumed that the duration of the pain syndrome directly depends on the mini-bleeding in ectopic foci and the accumulation of hemosiderin in them, which is macroscopically manifested by their brownish-bluish color ($p<0.001$).

(continue)

When assessing the results of histological examination in ectopic foci, the presence of focal lymphoid infiltration in them drew attention: in heterotopias in women of group I (EGE and CPPS), it was detected in 38.1% of cases, and in patients of group II – in 33.3%. However, there were no statistically significant differences in the study groups according to this criterion ($p>0.05$). Thus, the presence of lymphocytic infiltration does not correlate with the presence of pain syndrome and its severity, but the presence of an inflammatory component proves the formation of a nociceptive component of pain in these categories of women.

According to the results of the IHC study, it was noted that in the groups of patients with CPPS (group I) among lymphoid infiltration cells significantly dominated T-lymphocytes (CD3+), which amounted to 40 (abs. the number of cells in the field of view), whereas in women of group II of the study their number was equal to 11 (abs. number of cells in the field of view), $p<0.001$.

It should also be noted that in endometrioid foci in group I women, along with T-lymphocytes, b-lymphocytes (CD20+) were also significantly more often detected, which amounted to 79 (abs. the number of cells in the field of vision), whereas in group II patients their number was 15 (abs. number of cells in the field of view), $p<0.05$.

Thus, the results of histological and IHC studies revealed that women with EGE complicated by CPPS, ectopic foci in 93.3% looked reddish-bluish color with a high concentration of T- (40*) and (79*) lymphocytes in them ($p<0.05$), whereas patients with painless over negs visually were marked red (50%) and white (30%) lesions and brownish-bluish - only 20%, and the concentration of T- (11*) and (15*) lymphocytes was significantly less ($p<0.05$). (*Note: abs. number of cells in the field of view).

Thus, the results showed that the longer a patient with EGE has pain syndrome, the more often ectopic foci macroscopically have brownish-bluish color due to mini-bleeding and accumulation of hemosiderin in them, and also contain a significantly greater number of T - and B-lymphocytes, thus forming a cellular and humoral response ($p<0.05$).

In addition, the data obtained in the study indicate that there is no correlation between the severity of EGE and the severity of pain syndrome (with Spearman's rank correlation coefficient=0101). Perhaps this is due to the peculiarity of local macrophage activity in the foci of endometriosis.

Discussion

The results of our study suggest that the accumulation of hemosiderin as a result of mini-bleeding in ectopic foci, as well as local productive inflammation are the causes of the formation and maintenance of pain syndrome, and the rate of resorption of these foci depends on macrophage activity, frequency and severity of bleeding in the foci of EGE.

Thus, in the formation and progression of endometriosis lies the so-called abnormal immunological reaction associated with the body's response to the inflammatory agent, which, in fact, are endometrioid foci. There is no doubt that neoangiogenesis and neurogenesis are involved in the initiation and prolongation of local inflammation. However, the question of the root cause of these aberrant responses of the immune system remains unclear: whether initially endometriosis provokes its inversion work and subsequently leads to an increased cellular and humoral response, or whether its initial dysfunction is a predisposing factor to the formation and progression of endometriosis.

Undoubtedly, the expansion and addition of knowledge on local inflammation not only in the foci of endometriosis, but also in the areas around them, in the peritoneal environment, will help to determine the triggers in the early diagnosis of endometriosis, prevent the chronization and automation of pain syndrome, which will affect the selection of timely pathogenetic therapy not only of the underlying disease, but also its complications-chronic pelvic pain syndrome. The high degree of pain recurrence in women with EGE after surgical and long-term therapeutic management indicates the need for a new immunomodulatory strategy based on the normalization of cellular and humoral immunity.

Topic: 5.9 Pelvic pain

P261 A case of peritoneal tuberculosis difficulties of the differential diagnosis case

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Context

According to the US Centers for Disease Control and Prevention almost one third of the world's population is infected with tuberculosis which kills almost 2 million people per year. Abdominal TB continues to be a significant health problem in the developing countries.

Background

Female patients who present with ascites and adnexal tumors are presumed to have ovarian carcinoma. This can lead to radical surgery, hysterectomy with bilateral adnexectomy, with its associated morbidity. An important differential diagnosis to consider is peritoneal tuberculosis which can present in a similar manner and responds well to medical treatment only.

Case presentation: A 44 year old Caucasian woman, presented to our gynecology clinic with chronic pelvic pain, abdominal distension, weight loss and asthenia, sent to us from gastroenterology were she first addressed for these symptoms. Ovarian malignancy was highly suspected so she was operated. The extemporaneous exam of the right ovary with the cystic mass, hysterectomy with bilateral adnexectomy, revealed caseating granulomas with epithelioid cells and Langhan's type giant cells.

Conclusion

There are few features that suggest the diagnosis of peritoneal TB rather than ovarian carcinoma. Apart from chest X-ray findings which may not always be present, also CT can help in the differential diagnosis. PCR and ADA testing of ascitic fluid can also be helpful. When these tests are or negative unavailable then diagnostic laparoscopy or laparotomy is needed, because with the help of frozen section we can avoid unnecessary radical surgery in cases of peritoneal tuberculosis that responds to medical treatment only.

Topic: 5.10 Endometrial hyperplasia

P264 Vitamin D deficiency and chronic endometritis as predictors of endometrial hyperplasia

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Context

Vitamin D deficiency, thyroid dysfunction, obesity, chronic genital inflammation are pathogenetically associated with the development of dishormonal pathology of the reproductive system (Palacios C. et al., 2014; Holick M.F., 2015; Genazzani A. R., 2016). Risk factors for chronic endometritis are early sexual activity, genital infections, prolonged use of IUC, invasive intrauterine intervention. More than 90% of all cases of chronic endometritis occur in active reproductive age (25-35 years).

Objective

The study of the endometrium in women with chronic endometritis and vitamin D deficiency.

Methods

Hysteroscopy and morphological examination of endometrial biopsies were performed in 250 patients of reproductive age with suspected endometrial pathology. Chronic endometritis was verified by ultrasound, pathomorphological characteristics: plasmacytic-lymphoid infiltration; fibrosis, sclerosis of the stroma and endometrial vessels; immunohistochemical detection of CD138-positive cells. Immunohistochemical study of estrogen (ER), progesterone (RP), vitamin D (VDR) receptors was performed. Levels of 25(OH)D in serum were determined by CMIA. Assessment D status conducted under recommendations of Central Europe experts.

Results

Endometrial pathology was confirmed in 96.8% of cases, among them endometrial polyps - 13.5%, endometrial hyperplasia - 40.2%, polyps in combination with endometrial hyperplasia - 22.6%, endometrial mismatch to the phase of MC - 23.7%. The combination of chronic endometritis and endometrial hyperplasia occurred in 64.8%.

Vitamin D deficiency was detected in 83.3% of the examined cohort, severe vitamin D deficiency (25(OH)D 8.9±1.7 ng/ml) occurred in 11.2% of patients.

In all cases, an imbalance in expression of estrogen and progesterone receptors was noted. CD138 in the stroma of the endometrium were detected in 57.5%. In healthy women, at 90% of stromal cells and endometrial glands showed pronounced cytoplasmic expression of VDR. In cases of endometrial hyperplasia with chronic endometritis only in 60 - 40% of them revealed VDR expression. The presence of direct strong correlation r=0.815 between severe D-deficiency and the level of VDR expression in the endometrium was established.

Conclusions

An immunohistochemical study of endometrium in women with pathology of the endometrium and unrealized reproductive function allows you to optimize the complex of therapy and achieve the optimal endometrial state for conception of pregnancy.

Topic: 5.11 Endometriosis: genetics and hormones

P265 Estrogen-macrophages interplay as a possible therapeutic target in endometriosis

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Context

Endometriosis is an estrogen-dependent, chronic inflammatory disorder characterized by the growth of endometrial tissue in ectopic sites, causing pelvic pain and infertility. The ectopic endometrial tissue retains the ability to undergo remodeling during the menstrual cycle, but endocrine signaling is altered, being characterized by elevated estrogen levels and progesterone resistance. Endometriotic lesions are enriched in macrophages, which are insensitive to progesterone but responsive to estrogens, and operate in favor of lesion development as suggested by a derangement in immune polarization, phagocytosis and vascular activity.

Objective

In the present study, we compared the expression of estrogen receptors in peritoneal macrophages obtained from endometriosis and healthy women.

Methods

Peritoneal macrophages isolated from endometriosis patients were evaluated for the expression of sex steroid receptor genes by Realtime PCR assay.

Results

Our preliminary data show increased expression of the estrogen receptor GPER1 in peritoneal macrophages isolated from endometriosis patients, which also correlates with enhanced expression of genes related with macrophage polarization and endometriosis progression. Additional results will be discussed.

Conclusions

Current therapeutic interventions in endometriosis are based on progesterone, an offsignal of estrogen activation, to oppose estrogens actions in endometrial cells. Being insensitive to progesterone, macrophage responses to estrogens are probably unaffected by such therapies. Our data suggests the possibility of developing appropriate antagonists of macrophage estrogen signaling as novel therapeutic agents in endometriosis.

Topic: 5.11 Endometriosis: genetics and hormones

P266 Microscopic aspects of cervical endometriosis

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Introduction

Endometriosis is a benign pathology that can occur especially in women of fertile age. It can be accompanied by a complex symptomatology, or it can be asymptomatic. Endometriosis can be found in many areas, nearby: adenomyosis, endometriosis of the uterine appendages, or external: pelvic, colonic, abdominal wall endometriosis and so on.

Material and method

50 years old female patient presented in the Ambulatory Service for moderate vaginal bleeding and pelvic pain. The blood tests revealed mild anemia (Hb:11g/dL). The patient was hospitalized for specialized investigations and in order to establish the therapeutic management. Hemostatic and bioptic uterine curettage was performed. The ultrasound examination and the histopathological exam confirmed the diagnosis, endocavitary polyp and endometrial hyperplasia with atypia. Hysterectomy with bilateral anexectomy was decided as the best course of action. After surgery, the macroscopic exam found the existence of an endocavity polyp and an endometriosis site at cervix level. For certainty diagnosis the pieces were sent to the pathology center. The fragments were included in paraffin and analyzed at the microscope after Hematoxylin-Eosin staining and the immunohistochemical study with anti- α Estrogen Receptors (ER), anti- Progesterone Receptors (PR), anti-Cytokeratin 7 (CK7) and anti-Cytokeratin 20 (CK20) antibodies

Results

The macroscopic study demonstrated the existence at cervical level of an endometriotic cyst, with a chocolate aspect and an intracavitary endometrial polyp. The microscopic study with anti-ER / PR / CK7 antibodies revealed the presence of the endometrial glands in the cervix and the possible digestive appearance of the ectopic glandular tissue was denied.

Conclusions

The endometriosis focuses can have different localizations: in the myometrium, ovary, fallopian tubes, peritoneum, abdominal wall, but it can also have other localizations, such as the uterine cervix.

Topic: 5.11 Endometriosis: genetics and hormones

P267 Medroxyprogesterone acetate, dienogest and dydrogesterone have different effects on expression of inflammatory response genes in a model cell line of peritoneal endometriosis

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Context
The endometriotic microenvironment is characterised by increased concentrations of inflammatory molecules produced by immune cells and endometriotic tissue, which contribute to disease-associated chronic inflammation. Local inflammatory process is provoked by ectopic tissue implants and is suggested to have an important role in the genesis and development of the disease. Endometriosis is also characterized by diminished progesterone action, and therefore current treatments also include progestins, synthetic progestagens that mimic the effects of progesterone. While the anti-inflammatory effects of progesterone and progestins have already been reported in endometriosis, their influence on the global expression of inflammatory genes has not yet been examined.

Objective
The aim of this study was to evaluate the effects of three commonly used progestins, medroxyprogesterone acetate (MPA), dienogest and dydrogesterone, as a comparison to progesterone, at the molecular level.

Methods
We analyzed the effects of 100 nM progestins on the expression of 84 inflamatory genes in 12Z model cell line of peritoneal endometriosis using PCR arrays.

Results
The majority of the investigated inflammatory genes were expressed in 12Z cells and three genes, IL1R1, TNFRSF11B, and IL10RA, were significantly affected by treatment with progestins. Progesterone, MPA and dydrogesterone down-regulated IL10RA, MPA up-regulated IL1R1 and downregulated TNFRSF11B, while dienogest showed no significant effects on gene expression. Analysis of gene interconnections indicates that progesterone, MPA, and dydrogesterone can act via IL10 signaling pathway, while MPA can affect IL1, OPG/RANK/RANKL and OPG/TRAIL signaling pathways. These pathways can be associated with known positive effects, e.g. reduced lesion size, and known side effects, e.g. mineral bone density loss.

Conclusion
The results from the present study clearly indicate that progesterone and the progestins regulate the expression of inflammatory genes in distinct manners, and the association with known signaling pathways explains some of the activities that have been reported for individual compounds.

* *Contributed equally.*

Topic: 5.12 Adenomyosis

P268 Potential markers of early noninvasive diagnosis of adenomyosis

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Context
Adenomyosis is determined by the presence of ectopic mucosa within of the uterus, mainly in the myometrium. The problem of early diagnosis of adenomyosis is currently particularly acute, since there are still no reliable non-invasive diagnostic methods that could allow an accurate diagnosis and identification of adenomyosis in the early stages of the disease.

Objective
To study the features of the proteomic spectrum of peripheral blood and peritoneal fluid in women with adenomyosis.

Materials and methods
The study included 5 women of reproductive age with adenomyosis and 5 women without adenomyosis. The diagnosis of "adenomyosis" was confirmed by ultrasound, MRI, imaging of the uterus during surgical treatment with laparoscopic access and histological verification of the diagnosis after the operation. In the morning, on the eve of surgical treatment, all patients underwent peripheral blood sampling in the volume of 6 ml. Further, all patients underwent laparoscopy with peritoneal fluid sampling. The obtained biological fluids were centrifuged at 1500 vol./min for 15 minutes, with the aim of deposition of cellular elements and frozen at -80°C and stored until the time of the study. The proteomic spectrum of peripheral blood and peritoneal fluid of the women of the study groups was performed using mass spectrometric analysis.

Results
The study of peripheral blood revealed a group of proteins, the expression of which in patients with adenomyosis decreased compared to patients in the control group: heavy chain immunoglobulin γ-2, α-disintegrin and metalloproteinase with thrombospondin elements, afamine, serum paroxonase/aryltransferase, especially α-2 macroglobulin. In addition, a group of proteins was identified, the expression of which in patients with adenomyosis was increased: variable chains of the immunoglobulin λ 3-21, the heavy constant chain immunoglobulin μ, α-1-antichymotrypsin, α-2-antiplasmin, serotransferin. In the study of peritoneal fluid in patients with adenomyosis was found to increase the expression of only one protein: constant heavy chain immunoglobulin α-1.

Conclusions
The analysis showed the presence of proteins in peripheral blood and peritoneal fluid, characteristic only for adenomyosis and absent in the control group. And also proved to be more informative peripheral blood as a biological material of choice for early non-invasive diagnosis of adenomyosis.

Topic: 5.12 Adenomyosis

P269 The sonographic and symptomatic impact after combined oral contraceptive continuous regimens in adenomyosis patients

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Context
The use of combined oral contraceptive continuous regimens (COCCR) is nowadays increasing to treat adenomyosis (AD). However, it has been poorly researched.

Objective
To assess the sonographic and clinical changes after 1 year COCCR in AD patients.

Patients
200 patients diagnosed with sonographic AD were selected from the outpatient clinic. In order to be eligible, the patients had had to undergo 2 sonographic examinations, one before starting the COCCR treatment and a second after a follow-up period no shorter than a year. The impact of the treatment was measured in terms of number of sonographic criteria and symptoms present before and in a 12-month follow-up. Finally, 53 patients were evaluated.

Main outcome measures
The sonographic features of AD were reported following the Morphological Uterus Sonographic Assessment (MUSA) group consensus. One point was given for the presence of each of the 6 following criteria: hyperechoic islands, fan-shaped shadowing, asymmetrical thickening, translesional vascularity, cysts and interrupted junctional zone. The symptoms were evaluated using the visual analogue scale (VAS) (0-10) for dysmenorrhea and chronic pelvic pain. Severe symptoms were considered if scores of VAS ≥7.

Results
Results are expressed as mean+/-standard deviation (SD) or n(%). As expected, a significant reduction of dysmenorrhea from a VAS mean of 7.69+/-2.2 before treatment to 1.38+/-2.3 after treatment ($p<0.0001$) and VAS mean chronic pelvic pain from 3.9+/-2.9 to 0.51+/-1.1 ($p<0.0001$) was observed. A decrease in the number of patients with severe dysmenorrhea (before treatment: n=40 (75%); after treatment: n=3 (5%) [$p<0.0001$]) and chronic pelvic pain (before treatment: n=11(20%); after treatment: n=0 (0%) [$p<0.0001$]) was reported in the follow-up. Fourteen patients had heavy menstrual bleeding before the treatment and all achieved normal or decreased menstrual bleeding in the follow-up.
A significant decrease in terms of sonographic criteria present post-treatment was noted (before treatment: 3.9+/-0.9 and after treatment: 2.11+/-1.6 [$p<0.0001$]). A complete response to treatment with no sonographic signs of AD in the follow-up ultrasound was observed in 17 (32%) patients ($p<0.0001$).

Conclusion
There was a significant clinical improvement and a reduction of AD sonographic features COCCR after at one year follow-up. Further research with a longer follow-up, larger sample size and comparison with other AD treatments are needed.

Topic: 5.12 Adenomyosis

P270 Cystically transformed and fistulized adenomyosis - case presentation

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Introduction

Adenomyosis is a benign uterine pathology, represented by the presence of endometrial glands remote from the normal endometrium, in the myometrium structure. The incidence of this pathology is rising, being also a consequence of the cesarean section, by implanting endometrial glands in the neighboring structures or distant ones (endometriosis).

Clinical study and morphological aspects

A 39 years old patient presented in the Ambulatory Service for moderate vaginal bleeding, pelvic pain, dysuria. The patient was admitted in the 2nd Obstetrics-Gynecology Clinic of the Emergency County Hospital, Craiova for specialized investigations and therapeutic behavior. The common blood tests were within normal limits. At the ultrasound examination detected at uterine isthmus level a well-defined round, cystic tumor of 5/6 cm. This tumor was making common body with the external tunic of the urinary bladder. Surgical treatment was decided. Cystectomy was performed and the uterine isthmus was restored. The fragments were sent for histopathological examination.

The histopathological examination set the diagnosis, adenomyosis. In the classic Hematoxylin-Eosin staining, areas of fibro-collagen tissue were noted in the myometrium, groups of cystic dilated glands and endometrial stroma, with acute peri-glandular inflammation. The Immunohistochemical study with anti-Estrogen Receptors (ER) antibodies – positive reaction, anti-Progesterone Receptors (PR) – positive reaction, anti-Cytokeratin 7 (CK7) – positive reaction and anti- Cytokeratin 20 (CK20) – negative reaction, made the differential diagnosis with a possible metastasis that had a digestive starting point.

Conclusions

Adenomyosis is a benign pathology diagnosed with certainty through the histopathological exam, with multiple morpho-functional implications and sometimes very negative consequences on patients.

Topic: 5.13 Medical treatments for endometriosis

P271 Aspiration and Alcoholization of endometriomas guided by ultrasound prior to conceiving or assisted reproductive technology (ART)

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Context
Endometriosis is a complex gynaecological disease that affects 10-25% of women in fertile age. It involves pelvic pain, dyspareunia and infertility. Laparoscopy is the gold-standard diagnosis method and also the most used way of treatment. The therapeutical options include: hormonal treatment, surgical methods (laparotomy, laparoscopy) or both.

Objective
The aim of this study is to evaluate the efficacy of the aspiration and alcoholizaition of endometriosis cysts guided by ultrasound as a minimally invasive treatment alternative, especially in patients that want to conceive.

Methods
This study analyses and compares the results of the aspiration and sclerotherapy of endometriomas in patients in the period of January 2018 to December 2019 enroled in our clinic. All patients were followed clinically and by ultrasound after 1 month and 6 months.

Patients
19 patients diagnosed with endometriosis who had an endometrioma larger than 4 cm were included in the study. One of the inclusion criteria was desiring a pregnancy, either naturally or by assisted reproduction techniques.

Intervention
After using a GnRH agonist analog for at least 20 days, the cysts were punctured using ultrasound guidance and then the alcoholizaition was performed. The technique consists of ultrasound-guided vaginal cyst aspiration and injecting 95% ethanol into the cyst cavity.

Main outcome measure
A follow-up ultrasound examination was performed 1 month later. The patients were later divided into 3 groups: the first group: patients that chose to conceive naturally, the second group chose IVF and the third one decided not to conceive.

Results
The ovarian endometriosis cysts had an average diameter of 5 cm and did not recur after the aspiration. The frequency of symptoms (pelvic pain and dysmenorrhea) was significantly reduced after the procedure.
9 of 19 patients obtained a pregnancy after the procedure, 77,77% by IVF and 22,22% without any intervention.
There was no significant change in the mean serum level of AMH before and 6 months after the alcoholizaition. In some participants, serum AMH level increased after the alcoholizaition.

Conclusion
Aspiration followed by ethanol sclerotherapy can be a simple and effective option for patients who desire a pregnancy and have symptomatic or recurrent endometriosis cysts. The technique gives better short-term clinical results and helps preserving the ovarian reserve in patients with endometriosis that desire to conceive.

Topic: 5.13 Medical treatments for endometriosis

P272 Long-term evaluation of dienogest in the treatment of women with pelvic endometriosis

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Objectives

To construe the long-term clinical and laboratory effects of dienogest in women diagnosed with pelvic endometriosis.

Methods

Were included Sixty-one women diagnosed with pelvic endometriosis who used oral 2 mg dienogest tablets daily and who were treated for 48 months at the Women's Health Reference Center (Hospital Perola Byington), Sao Paulo, Brazil. All of the patients were analyzed for pelvic pain (dysmenorrhea and / or chronic pelvic pain) using visual analogue pain scale (VAS) in mm, and serum estradiol dosages in pg / mL and CA-125 in U / mL were performed., in the period of 0, 12, 24, 36 and 48 months. They were also evaluated for bleeding pattern: how many showed abnormal uterine bleeding and improved.

Results

Symptoms of chronic pelvic dysmenorrhoea or pelvic dysfunction at time 0, 12, 24, 36 and 48 months were 9.2, 4.1, 2.6, 2.1, and 2.1 mm, respectively. Serum estradiol dosages at time 0, 12, 24, 36 and 48 months were 55.8, 71.3, 85.8, 66.4, and 42.9 pg / mL, respectively. Serum CA-125 dosages at time 0, 12, 24, 36 and 48 months were 44.7, 22.9, 22.2, 20.6 and 24.2 U / mL, respectively. At the beginning of treatment, 25 patients (41%) had abnormal uterine bleeding, and at the end, all had a favorable bleeding pattern, reaching 69% of amenorrhea. Regarding menopause, 10 patients had laboratory confirmation during hormonal treatment.

Conclusion

Dienogest showed a good clinical response regarding painful symptoms and abnormal uterine bleeding in women with pelvic endometriosis, being well tolerated and it can be used with well-defined criteria over the long term, even until the menopausal transition. However, further studies should be performed to clarify its safety.

Topic: 5.13 Medical treatments for endometriosis

P273 Letrozole for successful medical management of sciatica due to extrapelvic endometriosis

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Introduction

Sciatica due to extra-pelvic endometriosis is rare and is suggested by cyclic nature of typical radiating leg pain that follows a dermatomal pattern along sciatic nerve distribution and is caused by compression of lumbar root or sciatic nerve or its plexus.

Case report

A 36 years old primipara presented with progressively increasing pain in right hip radiating to lower limb since 5 years that increased with menses. Since 3 years, she also reported weakness in right lower limb, loss of sensation in calf and foot drop. Patient had history of laparoscopy 4 years back when an inguinal lump was incidentally found and excised, histopathology of which revealed endometriosis. Since pain persisted, levonorgestrel-IUS was inserted 1 year back which did not relieve her pain. On examination, abdomen was soft, nontender, few nodularities were palpated in right inguinal region, P/V revealed normal size uterus, with tender right adnexa. MRI showed bulky uterus, bulky ovaries and a homogenously enhancing soft tissue was noted around sciatic notch involving sciatic nerve. Nerve conduction study showed distal asymmetrical, sensorimotor, large fibre axonal neuropathy in right sciatic nerve. Patient did not respond to LNG-IUS and dienogest 2 mg/day and reported only 25% reduction in symptoms at 1 month follow-up. Patient was started on oral letrozole with norethisterone, calcium and vitamin D. Her symptoms relieved within one month, hence her treatment was continued, which was stopped 1 and half year later. She underwent tendinoplasty for foot drop. Patient is in follow-up since two years after that and is asymptomatic.

Conclusion

Managing deep infiltrating endometriosis involving sciatic nerve is a challenge and requires multidiscplinary approach involving neurologist, neurosurgeon, radiologist and pain clinic. Letrozole is a boon for extra pelvic endometriosis as it prevents peripheral conversion to estrogen. Therapeutic trial may be given to such patients who would otherwise require extensive surgery for lesion excision.

Topic: 5.13 Medical treatments for endometriosis

P274 Deep infiltrating endometriosis as a cause of non-symptomatic hydronephrosis despite hormonal treatment and radical surgery in the centre of endometriosis

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Context

Endometriosis is a common gynaecological disorder that affects 5-10% of the population. In the majority of a patients endometriosis cause pain syndrome mostly perceived during menstruation and intercourse. Many patients suffer from reduced fertility. Severe disease including deep infiltrating endometriosis is relatively rare and creates often diagnostic and therapeutic challenges. Symptoms are organ-specific and depend largely on the site of infiltrations. The involvement of the urological tract rises severe complications that affect the patient's general health and quality of life.

Objective

Two cases with severe urogynecological complications including kidney loss after pharmacological therapy and recurrent surgical treatment of deep infiltrating endometriosis were analyzed.

Result(s)

Hormonal therapy and aggressive surgical treatment, especially when repeated, does not always stop the progression of the disease and fails in preventing surgery complication and further disabilities.

Conclusions

Careful clinical consideration has to be done to plan treatment strategy, pharmacological treatment, and extent of surgery in this multidisciplinary and complex disease. In many cases, hormonal therapy will be an effective and safest option for the patient. In some cases, a radical treatment including total hysterectomy with salpingo-oophorectomy and lesion resection in a multidisciplinary surgical team could be necessary. However, radical dissection increases the chances of recovery or long-term remission but is associated with an increased risk of serious complications such as collision with ureter and long-term complications. In some cases, treatment is unsuccessful, even if hormonal treatment was applied and radical surgery was performed. We present examples of ureter infiltration by endometriosis that caused non-symptomatic hydronephrosis and kidney function loss.

Topic: 5.13 Medical treatments for endometriosis

P275 Deep infiltrating endometriosis: evaluation of surgical complications and recurrence

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Contex
Endometriosis is characterized as the occurrence of endometrial tissue, outside the uterine cavity. Treatment for endometriosis fundamentally follows three principles: pain relief, improved fertility and prevention of disease progression or recurrence. Surgical treatment is the most recommended for complete endometriosis removal and is associated with an improved quality of life. However, this type of intervention still has a high morbidity rate and complications. In addition, surgical treatment has a high recurrence rate.

Objective
To evaluate the frequency and factors associated with complications of deep infiltrating endometriosis (DIE) surgery and its recurrence.

Methods
Retrospective study.

Patients
65 women with DIE. Interventions: surgery for treatment of DIE from 2007 to 2017.

Main outcome measure
The clinical characteristics of the women, the treatments used before and after surgery, the time of surgery and complications inherent to the procedure and disease recurrence were evaluated. Frequency, means and standard deviation of variables were calculated. To compare the variables, Fisher's exact test, Mann-Whitney test and Chi-square test were used.

Results
The mean age was 39.71 ± 6.31 years and the mean body mass index was 26.92 ± 5.05 kg / m2. The women had dysmenorrhea (91%), chronic pelvic pain (89%), dyspareunia (69%), pain to evacuate (41%), dysuria (23%) and infertility(44%). The mean duration of surgeries was 181.32 ± 65.70 minutes. The complications rate were 16.6% and associated intestinal involvement ($p = 0.01$), use of intramuscular progestagen ($p = 0.03$) and length of stay ($p = 0.01$). The recurrence rate was 34.7% and associated not using hormonal treatment after surgery ($p = 0.03$) and postoperative levonorgestrel intrauterine device ($p = 0.01$). Conclusion: The highest incidence of surgical complications occurs when there is intestinal involvement and recurrence of endometriosis is related to women who did not use any hormonal treatment after surgery or who used levonorgestrel intauterine device.

Topic: 5.14 Uterine myomas, medical and surgical

P276 A prospective comparative study for evaluation of ulipristal acetate and leuprolide acetate before performing outpatient hysteroscopic myomectomy

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Context

Outpatient hysteroscopic myomectomy can be usually performed in case of single submucosal fibroid with largest diameter up to 2 cm. The volume of the fibroid has a critical role in outpatient myomectomy as larger fibroids, requiring a longer resection time, may require less tolerated hysteroscopic procedures. Pre-operative hormonal therapy aims to decrease the volume of uterine fibroids.

Objective

This study aimed to compared outpatient hysteroscopic myomectomy performed by using the Versapoint system in patients having received 3-month pre-operative treatment with ulipristal acetate (UPA), leuprolide acetate (LA) or being undergone expectant management. The primary objective of the study was to compare the rate of complete resections in the three study groups. The secondary objective of the study was to compare the operative results between the study groups. The tertiary objective of the study was to assess the characteristics of the fibroids in patients treated with UPA and LA.

Material and methods

This was a single center prospective non-randomized study, including patients of reproductive age who required outpatient resection of single FIGO type 0-1 fibroid with largest diameter <2 cm.

Study patients underwent either preoperative treatment with UPA (5 mg/day; group UPA) or LA (11.25 mg/ml, group LA) for 3 months or immediate surgery (without pre-operative hormonal therapy, group S). The choice of receiving preoperative therapy was based on patients' preference. Hysteroscopic myomectomy was performed by using the Versapoint system.

Results

138 patients were enrolled in the study. The percentage decrease in the volume of uterine myomas was higher in group LA than in group UPA (p=0.015). Before surgery, fibroid volume was lower in group LA and in group UPA than in group S (p=0.026 and 0.043, respectively). The percentage of complete resection was significantly higher in group LA (83.0%; 39/47) than in group UPA (60.5%; 23/38; p=0.020) and in group S (62.2%; 33/53; p=0.021). The volume of fluid infused was significantly lower in group LA than in group S (p<0.005). The volume of fluid absorbed was not significantly different between the three study groups (p=0.341). The texture of the fibroids was more frequently rubbery or soft in group UPA than in the other two study groups.

Conclusions

In comparison with UPA or no treatment, LA improves the rates of complete resection in patients undergoing outpatient hysteroscopic myomectomy.

Topic: 5.14 Uterine myomas, medical and surgical

P278 Two steps procedure for hysteroscopic approach of submucosal fibroids

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Objectives

The aim of this study was to evaluate the use of transvaginal ultrasonography, diagnostic hysteroscopy and diagnostic and interventional hysteroscopy for the preoperative assessment of the uterine cavity in presence of submucosal fibroids.

Methods

A group of 141 of women, age 35-40, came for investigations, mostly for infertility and metrrogahea. In 78 cases there were fibroma between 2-3 cm diameter which were subserosal, with symptomology (bleeding, pain). 63 of them agree to the procedure of hysteroscpic removal in more than one step. It was performed a no touch hysterospy to evaluate the cavity. In 43 cases the fibromas were under 30% in the cavity type II (Wamstecker classification). We proposed a two or multi-steps procedure for fibroma removal with first step bipolar coagulation of the sub serosal capsule.

Results

In majority of the cases, after first menstrual bleeding the fibromas were pushed more in the uterine cavity (type 0 and I Wamstecker), which allowed interventional hysteroscopy to remove it in 1-2 steps. In 5 cases the coagulation of capsule was repeated and the fibroma arise after two or three menstruations, and in 8 cases the fibroma was not pushed into the cavity, where it was also an extensive adenomiosis of the uterus. In the follow up of the procedure was moderate bleeding after the coagulation of capsule, increased menstrual bleeding and pain during first menstrual bleeding after the procedure (more than usual) and repetitive procedures. The posterior wall fibroma was more easy to remove and required less steps of removal then the anterior wall fibroma.

Conclusions

The availability of advanced hysteroscopic surgical techniques has changed the management of abnormal uterine bleeding. Submucosal fibroma with small and medium dimensions can be removed hysteroscopically using multiple interventions steps on the basis of uterine physiology and before growing too much to avoid complications.

Topic: 5.14 Uterine myomas, medical and surgical

P279 Duplex scanning of the uterine artery in the diagnostics of uterine fibroid in women of the perimenopausal period

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Context
The frequency of fibroids in perimenopausal women in our region is up to 50.6%.

Objective
The role of duplex scanning of the uterine arteries in women with uterine fibroid of the perimenopausal period was studied.

Methods
The blood flow velocity curves in the uterine arteries and in the dominant myomatous node were analyzed with the determination of the blood flow velocity, RI, PI and the type of angioarchitectonics of the perifibroid plexus.

Patients
A prospectively nonrandomized case-control study, including 152 women, was conducted at the clinic of the Tashkent Medical Academy. Women were divided into 2 groups: the control group (n=50) and the group of women with fibroid (n=102). Interventions: duplex scanning of the uterine arteries.

Main outcome measures
The average age of the examined was - 50.1±0.74 years. The median uterine volume during US examination with uterine fibroids was 170.5 mm3, and in the control group - 52.1 mm3. In women with symptomatic uterine fibroid (n=53), the symptom of bleeding and anemia prevailed (83.01%).

Results
According to the duplex scan, the vascular parameters on the right and left did not differ significantly, the differences were found in the group with fibroid: the blood flow in the uterine arteries was higher in women with uterine fibroid 144.2±24.8 cm/s, ($p<0.001$) than in the control group (75.7±8.4 cm/s). The blood flow velocity in the perifibroid plexus with fibroid was higher than 72.1±22.1 cm/s ($p<0.001$). PI in the uterine artery in women with symptomatic uterine fibroid was 1.97±0.01 ($p<0.01$) than in the control group (2.47±0.8). PI in the perifibroid plexus was low ($p<0.001$). RI indicators: in the group of women with fibroid, it was 0.85±0.02 (in the perifibroid plexus was 0.76±0.03) ($p<0.001$) than in the control group (0.72±0.06). In duplex scanning of the perifibroid plexus, 4 types of angioarchitectonics were revealed in women with fibroid: the mixed (49.05%) and central type (28.3%) of the blood supply to the perifibroid plexus prevailed.

Conclusions
The presence of the clinic of the uterine fibroids may indicate a pronounced proliferative potential of the myometrium with these types of angioarchitectonics. In 1/3 of women with fibroid, an intense central blood flow in the nodes was an indication for surgical treatment. Depending on the type of blood supply to the node, an assessment is made of the growth of uterine fibroids, and a personalized approach to treatment is provided.

Topic: 5.14 Uterine myomas, medical and surgical

P281 Uterine lipoleiomyoma: a case report from the hospital of Lamia

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A uterine lipoma, is a benign lipomatous tumor, otherwise referenced to as fatty tumor of the uterus. It is an extremely rare case with its occurrence peaking at 0.12% of the population. A uterine lipoma usually affects postmenopausal women. No determination of the histogenesis of lipomatous tumors exists to date. Due to their fat content and rarity in occurrence these tumors usually get misdiagnosed when undergoing radiological examination. Uterine lipoma is preoperatively diagnosed via MRI although preoperative diagnosis is not commonly suggested and pathological examination might occur postoperatively in order to confirm the findings. A 64-year old woman in menopausal state with gravida 2 and para 2 came to the gynecology outpatient unit with complaints of irregular vaginal bleeding for a period of 9 months. There was no significant previous medical history. Clinical examinations were performed and the abdomen was found soft with a palpable mass of 5cm up to the pubic symphysis. Abdominal and pelvic ultra-sonography (US) was performed and revealed a heterogeneous echogenic mass in the uterine corpus of dimensions 8cm x 7cm x 9cm.

The ultra-sonography (US) exam was performed in order to measure endometrial thickness and the exam revealed an endometrial thickness of 4 to 5mm. For more medical imaging a pelvic MRI with intravenous was performed and revealed a mass 10cm x 11cm x 10cm which was similar to a uterine fibroma. A complementary examination for tumor markers CEA, CA15-3, CA19-9 and CA125 and Alpha-fetoprotein was also performed but was negative. Following the diagnostic procedure, dilatation and curettage were also applied and samples were sent for biopsy. The biopsy revealed atypical glandular cells of endometrial origin and the woman had to undergo total hysterectomy and bilateral adnexectomy.

The histopathology examination of the tumor from the uterine corpus revealed that the tumor was composed of lobules of mature antipodes separated by fibrous septae. In some places there were thin bundles of smooth muscle cells and normal blood vessels. There was no nuclear atypia or increased mitotic figures. Immunohistochemical stains such as smooth muscle actin (SMA, Desmin, AR, BR) were not performed. A diagnosis of lipoleiomyoma with total adipocyte degeneration or myometrial lipoma was made.

Topic: 5.14 Uterine myomas, medical and surgical

P282 Focused ultrasound fibroid thermoablation - a novel conservative perspective in fibroid therapy from first ultrasound-guided HIFU in Europ

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Context

Uterine fibroids are the most common tumors affecting approx. 40% of women of reproductive age. The prevalence rises with age. Fibroids change uterine structure and function, thus, they are a cause of infertility. Since reproductive plans are shifted to the fourth decade, uterine fibroids have become an emerging issue. Their high prevalence and benign characteristics imply that treatment could be low-invasive, and personalized to individual needs. Conservative treatment is targeted towards the maintenance and improvement of uterine function and is a method of the first choice in women of reproductive age and other women seeking low-invasive modalities. The novel, non-invasive method is percutaneous ultrasonographic termoablation (HIFU), that do not require even skin incision. Ultrasound beams remotely increase fibroid temperature, and finally, coagulation and aseptic necrosis occur.

Objective

We present our experience in the qualification and treatment of women with HIFU.

Methods

Patients had MRI before and after the treatment. The evaluation of the myoma number, size, localization, vascularisation, and their classification in FIGO and the Funaki system are invaluable for treatment. Symptoms, quality of life and bleeding were assessed by MPQ, VAS, SF-36, USF-QOL and MAC scales respectively. The analysis includes 65 patients, that after signing informed consent, were treated by HIFU with Alpius 900 (Alpinon). The total, perfused and non-perfused volumes of fibroids were measured by MRI.

Result(s)

Our results indicate therapeutic effect and symptoms alleviation in majority of cases. The proportion of ablated volume and effectiveness of treatment depended from fibroid distance from anterior abdominal wall, fibroid number, vascular perfusion and Funaki type. No significant adverse effects were observed in our cohort.

Conclusions

We noticed that HIFU procedure is very effective treatment of selected patients. Precise diagnosis and careful adherence to inclusion criteria warrant high effectiveness. Moreover, non-invasive procedure and high safety profile allow using the method in a wider spectrum of patients even those that do not adhere fully to all criteria. Current literature shows that HIFU has the best obstetrical outcomes compared to other methods. Treatment of symptomatic perimenopausal women gives a high chance of long-term recovery. Therefore the HIFU can be implemented principally before the pregnancy and in women before the menopause.

Topic: 5.14 Uterine myomas, medical and surgical

P283 Levonorgestrel intrauterine system (IUS) in treatment of leiomyoma and adenomyosis symptomatic women

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Women's Health Reference Center

Objectives

To evaluate use of levonorgestrel intrauterine system (IUS) in symptomatic women diagnosed with leiomyoma and adenomyosis.

Methods

50 women treated for 24 months with IUS containing 52 mg levonorgestrel and divided into 2 groups were analyzed: 27 women with leiomyoma (group 1) and 23 women with adenomyosis (group 2) at the Women's Health Reference Center (Perola Byington Hospital), São Paulo, Brazil. Pain was assessed by visual analog scale (VAS) in mm and abnormal uterine bleeding at times 0, 6, 12 and 24 months of treatment. Two patients (8%) from group 1 and 3 patients (14.3%) from group 2 excluded because they did not present clinical improvement after 12 months of treatment and were referred for surgical treatment.

Results

Dysmenorrhea and / or chronic pelvic pain were present in 18 patients (72%) in group 1 and 15 patients (71.4%) in group 2. Pain results (VAS) at times 0, 6, 12 and 24 months in group 1 were 8.1, 3.8, 2.8 and 2.2 mm, respectively; and in group 2 were 9.0, 4.6, 3.3 and 2.4 mm, respectively. In the end of 24 months, no patient reported significant pain (VAS <3 mm) in either group. Regarding abnormal uterine bleeding, 15 patients (60%) in group 1 and 12 patients (57.1%) in group 2 had some type of alteration. At the end of 24 months, all patients in both groups had favorable uterine bleeding (amenorrhea, infrequent bleeding, or monthly bleeding)

Conclusion

Clinical treatment with levonorgestrel IUS in women who diagnosed with benign diseases such as leiomyomas and adenomyosis and have clinical symptoms of pain or abnormal uterine bleeding may significantly improve through time, reducing the possibility of immediate surgical treatment, and reducing surgical risks and costs for medical institutions.

Topic: 5.15 Clinical management of adnexal cysts

P286 The evaluation of IOTA logistic regression model 1 (LR1) performance with the incorporation of HD-flow technique

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Aim

Differential diagnosis of ovarian tumor (DDOT) remains a recurrent problem in gynecological practice. Multiple predictive models, have been developed to facilitate the DDOT. Logistic regression model (LR1) by the International Ovarian Tumor Analysis (IOTA) group is one of such models. The model incorporate evaluation of tumor vasculature, however, the model was developed on the basis of old Doppler techniques (color and power-Doppler), and was not evaluated on modern techniques, such as HD-flow analysis. The main aim of our study was to evaluate the performance of LR1 model with the incoroporation of HD-flow tumor vasculature assessment.

Methods

The study group included 119 malignant and 85 benign patients diagnosed in Private Medical Practice Dariusz Szpurek due to ovarian tumor. The patients underwent ultrasound examination according to the IOTA group guidelines. The ultrasonography was performed using Voluson E6, with HD-Flow technique. All of the patients underwent adequate surgical treatment.

Results

In the group of benign ovarian tumors, we have identified 50 tumors with no blood flow (CD = 1), 23 tumors with minimal blood flow (CD=2), 8 tumors with moderate blood flow (CD=3) and 4 tumors with high blood flow (CD=4). The corresponding values in the group of malignant ovarian tumors were as follows: 20, 20, 34 and 45. The model achieved: the area under ROC curve of 0.901 (0.871-0.929), sensitivity: 86%, specificity: 76.3%, positive predictive value: 72%, and negative predictive value: 87%.

Conclusions

The evaluation of tumor vasculature by HD-flow technique represent adequate method for the use of LR1 model.

Topic: 6.1 Steroid hormones and ageing

P288 Follicular metabolic profiling in women of advanced and young ages under assisted reproductive technology treatment

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Context
Is there any difference between the metabolomic profile of the follicular fluid (FF) from the advanced maternal age women and those from the young control women?

Objective
The goal of this study was to detect biochemical profiles manifested human FF with the aim of identifying metabolic biomarkers of ovarian aging, the number of oocytes retrieved, and cleaved embryo numbers.

Methods
This was a prospective observational study.

Patients
Women seeking for *in vitro* fertilization treatment at the Women's Hospital, Zhejiang University from October 2014 to April 2015 were recruited for the present study.

Interventions
Fifteen women aged from 39 to 47 were grouped as advanced maternal age, and the other 15 women aged from 27 to 34, as young controls. Ovarian stimulation and oocyte retrieval were conducted using a regular protocol involving mid-luteal pituitary down-regulation and controlled ovarian stimulation.

Main outcome measures
The FFs from mature follicles were collected and centrifuged for analyses. Liquid Chromatography-Mass Spectrometry (LC-MS) and Gas Chromatography-Mass Spectroscopy (GC-MS) were used to perform the targeted quantitative metabolomic analysis. The FF levels of 311 metabolites and the metabolic significance were assessed.

Results
FFs from the two groups significantly differed with respect to 76 metabolites. FFs from the advanced maternal age group showed elevated levels of some amino acids (e.g., glycine, alanine, glutamine, histidine, lysine, tyrosine, valine, methionine, arginine, proline, and creatine), and reduced levels of N-acetyltryptophan, 3-methyl-2-oxovalerate, caprylate, acetoacetate, 3-hydroxybutyrate, pregnanediol-3-glucuronide, cortisol, and thymine. In subsequent correlation tests, we found 17 metabolites significantly correlated with maternal age, 6 metabolites correlated with the number of oocytes retrieved, and 10 metabolites correlated with cleaved embryo numbers.

Conclusions
This study corroborated successful determination of metabolites in human follicular fluids, and identified metabolic biomarkers of ovarian aging, the number of oocytes retrieved, and cleaved embryo numbers. The metabolomic signature of the follicular fluid reveals a significant increase in redox homeostasis and lipid metabolism, and decrease in steroid metabolites in the advanced maternal age women compared to young control women.

Keywords: Ovarian aging; Follicular fluid; Metabolomics; Biomarkers.

Topic: 6.1 Steroid hormones and ageing

P288b Characterization of vaginal and vulvar vestibule biopsies on healthy premenopausal women for the study of the vaginal and vulvar vestibule mucosae: a pilot study

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Context & Objective
It is generally accepted that the human genital tissues require both androgens and estrogens for adequate function. This view is supported by animal work, but human data is limited. We set out here to optimise biopsy sampling and processing that would allow the histological study of the human vaginal and vulvar vestibule mucosae.

Methods
Three types of tissue punches were assessed: Keyes punch, 90° angled Keyes punch, and Wittner punch. Upon collection, samples were formalin fixed and paraffin embedded for further processing. Morphological assessment of the biopsies was conducted using Masson's trichrome staining. Markers evaluated included the main sex steroids receptors and hydroxysteroid dehydrogenases, the 5α reductase and the aromatase.

Results
Four pre-menopausal women aged 38 to 47 years old and meeting the inclusion criteria received a vaginal biopsy. Two of them also received a vulvar-vestibule biopsy on a separate visit, providing a unique insight into the different characteristics of each location. The Wittner punch was found to be the most effective at getting a reasonably sized biopsy sample (~2 mm deep and ~5 mm wide) and keeping its morphology intact. Healthy epithelium and well blood-perfused dense lamina propria could be observed in all cases. Unfortunately, the muscularis was not reached. The enzymatic machinery necessary to the conversion of adrenal precursors such as DHEA into active sex steroids was mostly expressed in the epithelium, with the exception of the 5α reductase 2, known for converting testosterone to DHT, which was most detectable in the lamina propria, around capillaries. It was also possible to evaluate the distribution of the androgen receptor and the estrogen receptor α, which were unequivocally expressed in the vaginal and the vulvar vestibule's mucosae, mostly in the epithelium, but also in the lamina propria. Variable amongst patients, detection of the estrogen receptor β was either negative or very sparse and located in the vaginal epithelium, suggesting low expression.

Conclusions
While further studies are warranted to better understand the respective contributions of androgens and estrogens to the maintenance of healthy genital mucosae, we showed here that the human vagina and vulvar vestibule are lined with intracrinology-ready mucosae equipped to locally synthesize, and respond to, androgens and estrogens.

Topic: 6.1 Steroid hormones and ageing

P289 Vulvar vestibular effects of prasterone: a prospective vulvoscopic pilot study

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Context
Vulvovaginal atrophy (VVA), a component of the genitourinary syndrome of menopause (GSM), is estimated to affect about 60% of postmenopausal women. Key manifestations of VVA include dryness, burning and dyspareunia. In addition to reduced serum estrogen, low serum androgen levels may contribute to urogenital atrophy and impaired sexual function in postmenopausal women.

Objective
To examine, in menopausal women taking prasterone 0.50% (6.5mg) ovule daily, changes to the vulvar vestibule over 60 days using vulvoscopy in a prospective open-label pilot study

Methods
Women included in the study were postmenopausal with at least 1 year of amenorrhea and at least one moderate or severe symptom of VVA (vaginal dryness, burning, and dyspareunia). All participants received treatment with open-label, intravaginal administration of a 0.50% (6.5mg) prasterone ovule (suppository) once daily for 60 days.
The primary purpose of the study was to evaluate objective vulvoscopic changes by comparing each subject's baseline and end-of-study vulvoscopic photographs assessed using a 4-point rating scale which included observations for petechiae, pallor, friability, dryness, and redness in the mucosa (0, none; 1, mild; 2, moderate; 3, severe). The secondary objective were to assess for changes in symptoms of dryness, burning, and dyspareunia evaluated on a 10 cm visual analog scale (VAS).

Results
25 subjects met the inclusion and exclusion criteria and completed the study. The patients evaluated by the vulvoscopic photographs had a median score of 12.3 ± 2.31 points at screening and 5.2 ± 1.31 points at the end of the study (P =.02). After 60 days of therapy with prasterone ovule, there was a statistically significant decrease from the baseline in the mean scores for dryness, burning, and dyspareunia.

Conclusions
Prasterone ovule daily for 60 days showed improvement in physical examination findings in this prospective study of postmenopausal women with GSM symptoms, as documented on vulvoscopic photography. These changes were consistent with improvements in subject-reported pain and sexual function.

Topic: 6.1 Steroid hormones and ageing

P290 Association of the dehydroepiandrosterone sulfate levels and the ankle index - arm as a preacher of subclinical aterosclerosis in patients in the early posmenopause in the climate clinic of the Juárez Hospital of Mexico

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Introduction

Menopause reflects a progressive increase in cardiovascular diseases, where atherosclerosis is the main trigger. There is evidence of elevated levels of Dehydroepiandrosterone Sulfate (DHEAS) as a cardioprotective factor despite its diminution during menopause. Toshiyuki and colleagues proposed a cut-off value during early menopause of 126 ug / dl. The Ankle-Arm Index is a predictive tool of atherosclerosis, with 95% sensitivity and 99% specificity for obstruction of the vascular territory, a result equal to or greater than 0.9 being normal, lower results indicate arterial obstruction.

Objective

To determine the association of Dehydroepiandrosterone Sulfate Levels and the Ankle-Arm Index in the prediction of Subclinical Atherosclerosis in patients in the Early Postmenopause.

Study design

Prospective, cross-sectional and analytical study of cases and controls, performing a sample calculation with 95% confidence level and 7.5% margin of error, evaluating 132 patients in early spontaneous postmenopause, divided into 2 groups: 66 in the study group (DHEAS levels <126 ug / dl) and 66 in the control group (DHEAS levels> = 126 ug / dl). Both groups were assessed for weight, height, Body Mass Index, Waist-Hip Index, Ankle-Arm Index, Dehydroepiandrosterone Sulfate, glucose, Insulin, lipid profile, calculation of HOMA-IR and percentage of visceral fat. Association analysis was performed determining the Odds Ratio with SPSS software version 22.

Results

The average age of the control group was 51.46 years +/- 1.3, while in the study group it was 52.4 years +/- 3. Within the control group, 71% (n = 47) had an Ankle-Arm Index greater than or equal to 0.9, and 29% (n = 19) less than 0.9, compared to study group, 23% (n = 15) presented An Ankle-Arm Index greater than or equal to 0.9, and 77% (n = 51) less than 0.9. An Odds ratio of 8,411 was established, with a 95% CI (3.8-18.4), observing a strong association between both variables, being statistically significant (p = <0.05).

Conclusion

The association of the levels of Dehydroepiandrosterone Sulfate and the Ankle-Arm Index, proved to be very valuable tools that identify the patients who present with atherosclerosis in a preclinical phase. Dehydroepiandrosterone Sulfate can be considered a biomarker for the diagnosis and prevention of atherosclerotic disease during early menopause.

Topic: 6.1 Steroid hormones and ageing

P291 Predicting and preventing complication of PCOS, in order to achieve complete Quality of Family living (CQoFL)

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Context

The prevalence of PCO has been studied so much so that it ended with renaming of disorders by NIH, AE, ASRM. 50% to 75% were not aware of PCOs. The motivation was from red inverted triangle of family planning in 1975 now in infertility Center.75 % reports awaiting conception over 24 months and 20 % were PCOS. PCOS delayed parenthood and its odds ratio was 40 times on oligomenorrhea. ART by IVF risks in OHSS, for PCOs.

Objective

Primary: PCOS vs parenthood.
Secondary: Risk priority No (RPN) occurrence of menstruation interval, detection of hirsutism and severity of pain.
Usefulness of the study:
Preventing PCO's minimising cost and time.

Method

SEMMA
Sample from the challenged parenthood.
Explore: Failure Mode Effect Analysis by exploratory survey.
Modify: Life style modification and medicine (LSMM) from RPN.
Model: RPN without ultrasound where there is no phenotyping.
Assessment: Evidence based validation
The Intervention: RPN and LSMM
Main outcome of measurable: probability of PCOS and risk priority no.

Results

Maximum score for RPN at 1040 and the individual scores of 108 adolescents varied from 0 to 448 with an average of 37 following log normal pattern and RPN specified below 75. 11% diagnosed PCO and one unit of BMI increased the risk by 3 points and stress and depression, increased by 61 points.

Conclusion

PCOs clinically correlated to menstrual interval. Adolescent RPN above 75 were followed with LSMM resulting in parenthood.

Topic: 6.3 The climacteric syndrome

P292 KnowleDge of the genItourinAry synDromE of Menopause among Italian gynecologists: the DIADEM survey

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Context
Genito-urinary syndrome (GSM), which includes vulvo-vaginal and urinary symptoms, is a condition that affects postmenopausal women. However, according to many surveys it remains under-diagnosed and under-treated.

Objective
To evaluate the knowledge and attitudes of Italian gynecologists regarding GSM.

Method(s)
A survey was sent to 3892 gynecologists throughout Italy. The survey consisted of 30 multiple-choice questions divided into four different areas investigating: general demography of the responder, knowledge of the GSM, knowledge of its clinical management and patients' compliance and satisfaction about the current therapeutic option as perceived by the gynecologist.

Population(s)
Gynecologists both from private and public institutions from all over Italy.

Intervention(s)
An anonymous survey sent via electronic mail.

Main outcome measure(s)
Knowledge of GSM, most frequently prescribed treatments and compliance with the prescribed treatment according to the responder.

Result(s)
Three hundred and ninety gynecologists answer the survey. Three hundred and fourteen (84%) of them demonstrate knowledge of this condition and of the associated signs and symptoms. Almost half of participants (55%) consider GSM a condition affecting more than 40% of postmenopausal women. The majority of gynecologists (51%) believe that only 10-40% of postmenopausal women spontaneously report symptoms related to this condition. The therapy that gynecologists most frequently prescribe is local hormone therapy (61%) followed by moisturizers and/or vaginal lubricants (27%), ospemifene (10%) and laser therapy (2%). According to the clinical experience of participants, the most effective therapy is the local hormonal therapy (36%), followed by ospemifene (30%). According to the responders, less than 50% of the patients continue therapy after 12 months, mainly due to the discomfort in vaginal application, the cost of some therapies and the fear of possible side effects.

Conclusion(s)
This survey highlights an overall good knowledge of GSM among Italian gynaecologists. The most prescribed treatment for this condition is local hormone therapy that together with ospemifene is considered the most effective treatment. Gynecologists are aware that more than half of the patients discontinue therapies for different reasons.

Topic: 6.3 The climacteric syndrome

P292b Efficacy of 0.005% estriol vaginal gel through the initial days of treatment

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Context

Genitourinary syndrome of menopause (GSM) is a prevalent disease that can significantly impair health and quality of life of postmenopausal women. Non-reimbursed medications may result in an extra burden for certain women which together with a lack of prompt response may lead to discontinuation, more likely to occur initially. Choosing therapies that offer fast and effective relief is crucial in contributing to treatment success and meeting patients' expectations.

Objective

To assess the efficacy of 0.005% estriol vaginal gel through the first week of use.

Methods

Postmenopausal women with moderate to severe (M-S) VVA were enrolled in a multicenter 2-week prospective study. 34 patients received daily 1g of vaginal gel containing 50 µg estriol. Objective parameters (Maturation Value -MV-, superficial parabasal cells, pH) and vaginal signs were measured at baseline (bs) and days (d) 7 and 14. Symptoms (dryness, dyspareunia, pruritus, dysuria, lack lubrication) were registered daily and reported at weekly visits. Symptoms and signs were graded from 0=none to 3=severe. Global score of symptoms (GSSy, range 0-15) was determined. Mean (SD) and median (IQR) changes from bs were calculated; t-Student and Wilcoxon tests used for significance analysis.

Results

At d7 MV mean change from bs was 22.1(23.6), increasing its median pre-treatment value from 22.5 to 59.7 ($p<0.0001$). Changes in superficial cells and pH were 17.7(28.0) (from 2,7% to 20.4%) ($p<0.0001$) and 0.6(0.7) (from 6.3 to 5.8) ($p=0.0002$) respectively. Vaginal dryness (most bothering symptom) progressively improved from the first days (from severe to moderate after 1 dose, and to mild after 6). M-S vaginal dryness was referred by 94% women at bs and 41% at d7 (absent in 35%). M-S dyspareunia was referred by 83% at bs and 23% at d7 (absent in 38%). Overall, GSSy significantly improved, 24% women referred remission of all symptoms and 64% considered treatment relieved rapidly their symptoms.

Conclusions

Ultra-low dose estriol vaginal gel produced a rapid improvement of most relevant symptoms and signs of VVA, irrespective of their nature, severity or whether evaluated by physicians or patients. This clinically meaningful response was notable from the very initial days of treatment, confirming a substantial efficacy and a proved fast onset. To our knowledge this is the first and only local estrogen shown to provide a highly favorable clinical response as early as through the first 7d of treatment.

Topic: 6.3 The climacteric syndrome

P293 Relationships between climacteric syndrome, obesity and cardiometabolic biomarkers in postmenopausal women

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Introduction

Menopause is accompanied by a climacteric syndrome, leads to the development of central adiposity and an elevated cardiovascular risk.

Objective

To evaluate the relationship between climateric symptoms, obesity, and cardiovascular biomarkers in postmenopausal women.

Methods

228 postmenopausal women (57.65±6.42 years), were divided into quartiles according to their waist circumference (WC); Qu1: 83.50 ± 4.68 cm, Qu2: 93.91 ± 2.51, Qu3: 103.07 ± 2.55 and Qu4: 114.07 ± 4.82 cm. Climacteric syndrome was evaluated by an adapted questionnary. In serum, were analyzed lipid profile, C-reactiv protein (CRP). Pro-oxidant status was assessed by thiobarbituric acid reactive substances (TBARS) and protein carbonyls analysis and antioxidant defense by superoxide dismutase (SOD) and catalase (CAT) activities evaluation. Bivariate analysis was assessed by U Mann Whitney test.

Results

Sleep disturbances affect 47.9% of women, 8.80% in Qu1, 11.40% in Qu2, 12.30% in Qu3 and 15.40% in Qu4. More than 50% of women were tired; 11% in Qu1, 13.20% in Qu2 and Qu3 and 14.90% in Qu4. Compared to Qu1, CRP values were increased by +32.24% in Qu2, +61.22% in Qu3 and more 2-fold higher in Qu4. TBARS increased by 41% in Qu2 ($p<0.01$), +43.92% ($p<0.01$) in Qu3 and +65.42% in Qu4 ($p<0.001$). LDL-TBARS were increased ($p<0.001$) in all quartiles. Carbonyls concentrations were 1.38-fold more elevated in Qu2 ($p<0.01$), 1.35-fold in Qu3 ($p<0.001$) and 1.39-fold in Qu4 ($p<0.001$). Significant decrease ($p<0.001$) in SOD activity was noted in Qu2 (-17%), Qu3 (-34.55%) and Qu4 (34.31%). Catalase activity decreased significantly in all quartiles ($p<0.001$). Some climacteric symptoms (hot flushes, heart palpitations, sleep disturbances, venous insufficiency...) were associated positively with WC ($p<0.05$). Poor sleep quality and hot flushes were positively correlated with total cholesterol, CRP, TBARS-LDL and carbonyls. Hot flashes were inversely correlated with SOD activity ($p<0.001$).

Conclusion

In post menopausal women, climacteric syndrome was correlated with central obesity, inflammation and oxidative stress enhancing cardiovascular risk.

Topic: 6.3 The climacteric syndrome

P294 Epidemiology of natural menopause and climacteric syndrome in the East Siberian population: age and racial aspects

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Objectives
To determine the age- and race dependent characteristics of menopause and climacteric symptoms in an unselected population of advanced-age women from Eastern Siberia.

Methods
We recruited 1362 women, aged 51.31 (7.96) years, during the institution-based, cross-sectional study, performed in 2016-2018, in 2 cities and 1 rural area (Irkutsk region, Buryat Republic, Eastern Siberia, Russian Federation). Among 1362 examined women, 873/1362 were Caucasians (64.1%), 411/1362 (30.2%) - Asians, and 78/1362 (5.7%) - of mixed-race. All women wrote informed consent. The study was approved by the local ethics committee. The exclusion criteria were as follows: a) current pregnancy or lactation (for pre-menopausal subjects); b) history of hysterectomy, bilateral oophorectomy, endometrial ablation, and/ or uterine artery embolization. All women underwent a standard medical examination and pelvic ultrasound. “Natural” or “spontaneous” menopause was defined as a clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 months in a previously cycling woman, in the absence of surgery or medication. The climacteric symptoms were estimated by the MRS questionnaire. We performed statistical analysis using t, U and $\chi 2$ criteria. Data presented as n/N (%) and Mean (Std). P-value < 0.05 was considered as statistically significant.

Results
Of 1362 examined women menopause has been reported in 604 subjects (46.1%): in 413/873 (47.3%) of Caucasians, 192 /411 (46.7%) - Asians, and in 30/ 78 (38.5%) women of mixed-age. The number of post-menopausal women in the groups of different age was as follows: 14/399 (3.5%) in 40-45 years old women, 71/292 (24.3%) -in 46-50 years old, 178/ 248 (77.8%) and 372/423 (87.9%) in subjects aged 51-55 and older than 56, accordingly (all $p<0.01$). The total MRS score was 8.50(5.76) in the group of younger women (aged 40-45 years) and did not increased significantly by the age 46-50 (8.43±6.16) years. Among the subjects aged 51-55 years the mean total score was 9.90±6.32 and reached 10.43±6.77 after 56 years.

Conclusions
There was no race difference in menopausal women proportions, at the same time, we have demonstrated the lowest prevalence of women with reported menopause at 40-45 years, and the highest one - after 56 years. Therefore, the race-dependent aspects of menopause require further investigation, taking into account all potential co-founders.

Topic: 6.3 The climacteric syndrome

P295 Depressed symptoms and related factors in mid-aged women from Paraguay

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Objective

To determine the prevalence of depressive symptoms and related factors among mid-aged women.

Methods

This was a cross-sectional study in which 216 urban-living women from Asunción-Paraguay (aged 40–60 years) were surveyed with the 10-item Center for Epidemiological Studies Depression Scale (CESD-10) and a questionnaire containing personal and partner data.

Results

The median age of the sample was 48.7 ± 6.1 years, 48.1% were postmenopausal, 8.8% used hormone therapy, 39.4% psychotropic drugs, 43.5% had hypertension, 6.5% diabetes, 44.9% abdominal obesity, and 89.3% had a partner (n=193). Mean total CESD-10 score was 5.8 ± 5.6 and 25.5% of women had total scores 10 or more defined as depressed mood. Overall, 93.3% (180/193) of women having a partner were sexually active, with a median coital frequency of 8 times per month. Factors associated with higher CESD-10 total scores were: female age, educational level, marital partner status, menopausal status, psychotropic drugs, oral contraceptive use, sedentary lifestyle, partner age, coital frequency, erectile dysfunction and premature ejaculation.

Conclusion

As determined with the CESD-10 a quarter of this mid-aged urban female Paraguayan sample had depressed mood which was related to sexual, hormonal, partner issues, and other female aspects.

Topic: 6.3 The climacteric syndrome

P298 Correlation between body fat content and climacteric symptoms in Chinese menopausal women

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Objective

To explore the correlation between body fat content and related clinical manifestations using the modified Kupperman score for Chinese menopausal women.

Methods

113 patients with climacteric symptoms who were treated from February 2019 to August 2019 in the endocrinological clinic of the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, were investigated, in terms of the systemic body fat content (measured by bioelectrical impedance technology) and correlated with the modified Kupperman score (hot flushes, sweating, sensory disturbances, insomnia, depression, anxiety, dizziness, fatigue, muscle and joint pain, headache, palpitations, formication of the skin, sexual life, urinary irritation symptoms). The data were analyzed by non-parametric correlation analysis (Spearman correlation analysis) and multivariate logistic regression analysis to study the correlation between the above indicators of patients and each symptom in the modified Kupperman score.

Results

The average age of patients was 51 ± 5.19 years. Non-parametric correlation analysis: Systemic fat content was significantly positively correlated with depression ($r = 0.254$, $P = 0.008$) and urinary irritation ($r = 0.312$, $P = 0.001$); there was no significant correlation between systemic fat content and hot flashes ($r = 0.084$, $P = 0.389$), sensory disturbance ($r = 0.054$, $P = 0.580$), insomnia ($r = 0.095$, $P = 0.329$), anxiety ($r = 0.123$, $P = 0.206$), dizziness ($r = 0.075$, $P = 0.437$), fatigue ($r = 0.123$, $P = 0.205$), muscle and joint pain ($r = 0.016$, $P = 0.871$), headache ($r = -0.048$, $P = 0.619$, palpitations ($r = 0.070$, $P = 0.469$), formication of the skin ($r = 0.164$, $P = 0.090$) or sexual life ($r = -0.181$, $P = 0.059$). Multivariate logistic regression analysis: Systemic fat content was an independent risk factor for depression symptoms in menopausal women (OR = 1.074, 95% CI = 1.014 ~ 1.138).

Conclusions

In our study increased systemic fat content was associated with higher frequence of depression and urinary symptoms, which should be taken seriously in account during clinical work with menopausal Chinese patients. Other symptoms described within the modified Kupperman score do not seem to have a direct relationship to systemic fat content.

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Funding: Beijing Municipal Administration of Hospitals Clinical medicine Development of special funding support, code: XMLX201710; Beijing Municipal Administration of Hospitals'Ascent Plan, code: DFL20181401

Topic: 6.4 Menopause, HRT and CVD

P299 A phase 3 protocol to assess the efficacy and safety of estetrol (E4), a promising new treatment for menopausal vasomotor symptoms

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Context

Estetrol (E4), a natural estrogen, has promising therapeutic value. A Phase 2 dose-finding study showed that E4 15 mg is effective for the treatment of postmenopausal (PM) vasomotor symptoms (VMS) with beneficial or unchanged hemostatic, lipid, and glucose homeostasis parameters. There were no adverse events noted. Here we present the design of two pivotal phase 3 trials for VMS in PM women; one trial is to be conducted in the EU, Russia and Latin America (trial E4Comfort I), and one to be conducted in the USA and Canada (trial E4Comfort II).

Methods

Advice was obtained from experts, investigators, and regulatory bodies including the FDA and EMA. In 2019, the protocols were developed and submitted for approval to local regulatory agencies and/or ethics committees.

Results

Both trials have a placebo-controlled, multicenter, randomized design and will evaluate the efficacy and safety of E4 for the treatment of moderate to severe VMS in PM women, 40-65 years of age. Both trials have two study parts: an Efficacy Study, and a Safety Study. The Efficacy Study will enroll approximately 600 hysterectomized (H) and non-hysterectomized women (NH) with moderate to severe VMS (VMS (>=7 VMS/d, >=50 VMS/w) and receive (double blind) E4 (15 mg or 20 mg), or placebo in a 1:1:1 ratio for 12 weeks. Efficacy will be assessed by mean change in weekly frequency and in severity of moderate to severe VMS from baseline to week 4 and 12. The Efficacy Study, E4Comfort II, will continue for 40 weeks for safety assessments.

The Safety Study will include women seeking treatment for VMS (>=1 moderate to severe VMS per day). E4Comfort I will enroll approximately 600 NH women for endometrial safety assessment; they will receive (open label) 20 mg E4 and 100 mg progesterone (P4) for a period of 52 weeks. E4Comfort II will enroll approximately 200 H and 200 NH women who will receive (open label) 20 mg E4 for a period of 52 weeks. Endometrial safety of all NH women participating in the trials will be monitored by endometrial biopsy at baseline and end-of-trial, as well as by endometrial thickness assessments (at 3, 6, and 12 months) and daily recordings of vaginal bleeding events.

Conclusion

The E4Comfort Study II started in September 2019; the E4Comfort Study, in December 2019. With the expectation that good efficacy and safety data will be available from the E4Comfort Study I and II trials, E4 will offer a novel treatment for symptomatic PM women.

Topic: 6.5 Menopause, HRT and cancers

P299b Absence of detrimental impact of treating women diagnosed with vulvovaginal atrophy (VVA) with intravaginal prasterone (DHEA) on the risk of breast cancer: a retrospective matched cohort study

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Objective
Intravaginal prasterone is the only prescription therapy approved by the FDA for the treatment of VVA symptoms without a boxed warning for the risk of breast cancer (BrCa). The objectives of the study were to assess the 1-year incidence rate and 1-year recurrence rate of BrCa among women treated with prasterone compared to matched controls of untreated VVA women.

Methods
This retrospective cohort analysis was conducted using data from the Integrated Dataverse (IDV) database from Symphony Health Solutions (02/2015 to 01/2020). Women were required to have at least 12 months of medical/pharmacy activity before and after the first observed dispensing for intravaginal prasterone 6.5 mg (Intrarosa®, Millicent) or first VVA diagnosis (DX) (index date). Among women without history of BrCa, incident cases were identified as women with at least one DX for BrCa during the 12 months after the index date. Among women with history of BrCa, recurrent cases of BrCa were identified during the 12 months after the index date. In both cases, women treated with prasterone were matched 1:1 to untreated VVA women with respect to calendar year and age (at index date), cancer DX, BrCa DX, use of chemotherapy, family history of BrCa, use of estrogen therapy, mammography, obesity and hyperlipidemia (prior to the index date), and Charlson Elixhauser comorbidity index (assessed during the 12 months prior to the index date).

Results
47,118 patients treated with Intravaginal prasterone were matched 1:1 with untreated VVA women for the incidence analysis while 2,742 prasterone-treated patients were matched 1:1 with untreated VVA women for the recurrence analysis. Incidence rate of BrCa during the 12 months following the index date in treated patients was 0.39 % Vs 0.44 % for matched controls (p=0.2643). Recurrence rate of BrCa in treated patients during the 12 months following the index date was 34.21 % Vs 40.37 % for matched controls (p<0.0001).

Conclusions
While the results are based on retrospective data, they nonetheless highlight the absence of a manifest detrimental impact of the use of intravaginal prasterone on neither the incidence nor the recurrence of BrCa in women with VVA, but also the growing use of intravaginal prasterone in US BrCa patients, thus permitting the inclusion of almost three thousand patients with a history of BrCa in that study. Sensitivity analyses stratifying on cumulative days of supply also showed an absence of detrimental effect.

Topic: 6.5 Menopause, HRT and cancers

P300 Premature ovarian insufficiency in BRCA genetic mutation

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Context

Women who carry a BRCA mutation have an increased risk of developing breast and ovarian cancer. Recent studies have suggested that women with BRCA 1 and 2 mutation have a higher risk of early menopause or occult primary ovarian insufficiency, which has significant clinical implications. Our attention was drawn to this entity by two identical twins, aged 34, admitted to our clinic for POI.

Case report

Menarche occurred at the age of 11 for both twins. One twin had periods every 28 days and the other every 21 days. One twin gave two births, the other one gave one, they both had boys and breastfed them. The first twin had her last period at the age of 33, the second one at the age of 32. Both twins experienced menopausal symptoms. Due to the positive family history for breast and ovarian cancer, genetic tests were performed and a positive BRCA mutation was found, which is why a prophylactic bilateral mastectomy was performed on both twins at the age of 31.

The genetics findings were lost, so it is unknown whether they are BRCA 1 or BRCA 2 positive.

The twins do not remember their mother, since she died at the age of 38 after ovarian adenocarcinoma. The mother was Slovak. Mother's sister died of breast carcinoma at the age of 36 and a cousin on the mother's side died at the age of 39 of ovarian carcinoma, whereas another sister of their mother is healthy. The relatives on the mother's side died in their 40s of unknown causes. Sex hormones indicate hypergonadotropic hypogonadism in both. Breast and transvaginal ultrasound were clear for both of them. Bone density was decreased in both patients. Genetic analyses were performed for BRCA and a mutation was found in the BRCA 1 gene, which was a transversion of thymine into guanine at codon 181. After a conciliar decision, a prophylactic laparoscopic bilateral adnexectomy was performed. Pathohistological finding were benign for both. Transdermal menopausal hormone therapy by oestradiol and cyclic micronized progesterone was introduced postoperatively.

Conclusions

Women who carry the BRCA mutation are at increased risk of POI. BRCA carriers should be advised not to delay pregnancy. Family history for breast and ovarian cancers in females and breast and prostate cancers in males is crucial for suspicion and diagnosis of asymptomatic BRCA mutation carriers.

BRCA carrier should undergo thorough genetic counseling at the time of diagnosis that should also include fertility considerations.

Topic: 6.5 Menopause, HRT and cancers

P300b Intravaginal prasterone (DHEA) does not increase serum levels of estrogens in women treated with an aromatase inhibitor for breast cancer - results from a pilot study

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Objective
Hormonal treatment options for vulvovaginal atrophy in women with a history of breast cancer are limited. Intravaginal prasterone 6.5 mg is the only prescription therapy approved by the FDA for the treatment of VVA symptoms without a boxed warning for the risk of breast cancer. The objective of this study was to evaluate the time course of prasterone compared to placebo on the serum levels of DHEA and its metabolites in women treated with an aromatase inhibitor for breast cancer.

Methods
This study was a randomized, double-blind and controlled, cross-over study. Patients were randomized to receive, on Day 1, a single intravaginal insert (ovule) of prasterone (Intrarosa®) or placebo. Seven days later, the women who first received a prasterone insert would receive a placebo insert, and vice-versa. Blood samples were obtained at specific time intervals over a 24h period after prasterone or placebo administration for measurement of the serum levels of DHEA and its metabolites by using validated LC-MS/MS methods.

Results
Three patients treated with an aromatase inhibitor for breast cancer who have moderate to severe symptoms of vulvovaginal atrophy (VVA) were randomized in this study. Following administration of either the placebo or the prasterone insert, two out of three patients had undetectable levels of estradiol (< 1 pg/ml) and estrone sulfate (< 40 pg/ml) at all time points while the third patient had barely detectable levels of estradiol (Cmax = 1.3 ±0.26 pg/ml with prasterone VS Cmax = 1.2 ±0.24 pg/ml with placebo) and estrone sulfate (Cmax = 51.5 ±10.3 pg/ml with prasterone, and Cmax = 50.7 ±10.1 pg/ml with placebo). All three patients had levels of estrone below the limit of quantitation (<4 pg/ml) with both prasterone or placebo throughout the study.

Conclusion
These data show that the serum levels of estrogens remain undetectable or very low following the administration of a single intravaginal dose of 6.5 mg of prasterone in women taking an aromatase inhibitor. Although the number of patients is very limited, these results suggest that intravaginal administration of prasterone may be a safe treatment option for VVA in women with a history of breast cancer taking aromatase inhibitors.

Topic: 6.7 Postmenopausal osteoporosis

P301 The influence of the menopause onset time on low-energy fractures in women aged 50 years and older in Belarus

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Objective

The aim of this retrospective, single-center, non-interventional study was to evaluate features of the development of low-energy osteoporotic fractures in women aged 50 years and older depending on the age of menopause onset.

Methods

We have analysed data from personal questionnaires of out-patients about site (localization) and age of low-energy fractures after 50 years old. The measurements of T-score neck of the hip (NH) and T-score lumbar spines (LS) was done by DEXA (GE Lunar, USA). Exclusion criteria: age younger than 50 years old and high-energy fractures. Statistical analysis was performed with the calculation of Chi-square test, Student's t-test and a p value less than 0.05 was regarded as statistically significant.

Patients

Women aged 50 years and older with a diagnosis of osteoporosis according to DEXA data by WHO criteria with or without low-energy fractures and women with low bone mass after low-energy fractures (forearm, proximal femur and spine).

Results

The study included 3,086 women aged 66.1 ± 8.8 years (from 50 to 90 years). The group of interest (Gr_1) consisted of 805 women whose menopause onset was 45 years old and early. In the comparison group (Gr_2) was included 2,281 woman whose age at menopause was more than 45 years. The mean age and BMI in the groups did not differ significantly ($p>0.05$). The frequency of patients number with fractures in the groups was equal: 26.0% (n=209) in Gr_1 and 27.8% (n=633) in Gr_2 (chi sq = 0.87; $p = 0.351$). We also didn't obtain statistically significant differences in the mean values in the groups of the T-score NH and the T-score LS ($p> 0.05$). It was found that the average age of the onset of the first fracture in Gr_1 was less than in the Gr_2 group (58.8 ± 8.5 vs 61.8 ± 8.4; $p <0.01$). At the age of 50-59 was registered 51 (24.4%) fractures in Gr_1, which is significantly higher (chi sq = 4.81; $p = 0.028$) than in Gr_2 (n = 109; 17.2%) in the same age period.

Conclusion

In patients aged 50 years and older with early menopause, the average age of occurrence of low-energy fracture due to postmenopausal osteoporosis is less than in patients without early menopause and every fourth fracture occurring before the age of 60 years old.

Topic: 6.7 Postmenopausal osteoporosis

P302 Influence of central adiposity on the association between uric acid and bone health in postmenopausal women

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Context

Recent studies have positively correlate serum uric acid (SUA) with bone mineral density, however not properly measured gender-specific confounding factors led to conflicting results.

Objective

To investigate the relationship between SUA, bone health and the potential influence of body fat mass and menopause on this interplay.

Methods

Bone mineral density (BMD) and markers of bone metabolism were assessed in 124 pre-menopausal and 234 post-menopausal women. We examined whether SUA is related with (I) BMD at different skeletal sites and (II) with markers of bone metabolism. Furthermore we investigate whether this relationship is influenced by central adiposity, as assessed by anthropometry and dual x-ray absorptiometry (DXA).

Results

After conservative adjustment (covariates: age, hormones treatment, smoking and time since menopause), SUA showed a significant and positive association with total hip BMD (β=0.220, $p<0.01$) only among postmenopausal women. The association were confirmed also after adjustment for legs adiposity. Notably, the stratification for waist circumference (WC) quartiles revealed significant correlation between SUA and total hip BMD (r=0.444, p=0.001) in the highest quartile (91-100 cm). This association was independent of body mass index but dependent of DXA-derived indices of total or central fat mass.

Conclusion

Our results suggest that SUA is highly influenced by the amount of central adiposity in postmenopausal women. SUA might be beneficial for bone health during menopausal transition, however, the definitive appreciation of the association between SUA and BMD require further longitudinal studies that should include indices of abdominal fat as covariates.

Topic: 6.7 Postmenopausal osteoporosis

P303 Vitamin D and the musculoskeletal disorders in menopause

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Context

An adequate level of calcitriol (1,25-dihydroxy-vitamin D3) is essential for maintaining and maintaining good health. Calcitriol (the active form of vitamin D) has an effect on about 200 genes (accounting for about 5% of the human genome) and on 36 different tissues. The bone and the bone system are one of the target tissues of Vitamin D. Insufficient vitamin D levels are associated with bone density loss and the occurrence of osteoporosis. It also has a direct effect on muscle cells via the vitamin D Receptor (VDR) in muscle cell nuclei. Affects muscle cell contractility, muscle strength, and postural stability. The deficiency of this important hormone affects the occurrence of sarcopenia.

Objective And Methods

Menopausal women, 45-70 years of age, were included in the study. They were measured by Dual-energy X-ray absorptiometry (DXA) apparatus: bone density (BMD), skeletal muscle mass (SMM), and appendicular muscle mass (AMM). The level of 25-hydroxy-vitamin D (25 (OH) D) was determined. To assess the presence of sarcopenia, a muscle strength test was performed using a Hand grip test (HGT).

Results

The mean age of women was 57.16 ± 5.71 years. The onset of menopause in the subjects was 49.59 ± 4.02 years. Menopause duration averaged 7.51 ± 4.99 years. The mean value of 25 (OH) D was 39.43 ± 16.73 nmol / L. There were no subjects with normal vitamin D. Vitamin D insufficiency was 76.2%. Patients had osteopenia (BMD L1-L4 0,889kg / m^2; BMD neck 0,686kg / m^2; BMD tot-hip 0,845kg / m^2). The average muscle strength was 12.44 ± 2.24 kg and was statistically significantly lower than the norms for age ($t = -21.65$; $p < 0.001$). Cut-off value for reduced muscular strength for women HGT <20 kg and dynapenia was confirmed in our patients. The skeletal muscle mass index (SMI) was 6.72 ± 0.91 kg / m^2. For confirmation of sarcopenia in women, the cut-off is an SMI <5.25 kg / m^2. We doesn't confirm sarcopenia in our subjects. A positive correlation was found between 25 (OH) D and muscle strength test ($R = 0.227$; $p = 0.022$).

Conclusions

Our menopausal subjects had vitamin D deficiency associated with decreased bone density - osteopenia, decreased muscle strength - dynapenia. They had a reduced level of skeletal muscle but did not have sarcopenia. Vitamin D affects the musculoskeletal system and is an important predictor of its preservation during menopause.

Keywords: 25-hydroxy-vitamin D, osteopenia, dynapenia, menopause

Topic: 6.9 Selective estrogen receptor modulators SERM's

P304 Effects of SERMs on bone health in postmenopausal women

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Objective
Most selective estrogen receptor modulators (SERMs), via binding to estrogen receptors, act as estrogen agonists in bone, and some are approved for the prevention and/or treatment of postmenopausal osteoporosis. Here we review clinical, skeletal effects of SERMs in postmenopausal women.

Methods
PubMed was searched for journal articles published in English using keywords of raloxifene (RLX), bazedoxifene (BAZ), ospemifene (OSP), or lasofoxifene (LAS), and bone. Primary clinical studies on bone mineral density (BMD), bone turnover markers (BTMs), or fracture prevention in postmenopausal women with no major co-morbidities were included. Studies comparing or combining SERMs with other therapies were excluded.

Results
Retrieved publications reported studies demonstrating that RLX, BAZ, and LAS, SERMs approved for postmenopausal osteoporosis prevention and/or treatment, significantly increased BMD.1-6 Multiple studies also showed significantly reduced risks of new vertebral fractures with RLX or BAZ, while changes in nonvertebral fracture risks were not significant.2-4,7 A large, randomized trial showed significant risk reduction of vertebral and nonvertebral fractures with LAS.8 Reports following BAZ or RLX use for 7–8 years revealed their long-term efficacy on bone health.5,7 SERMs with bone indications (RAL, BAZ, LAS) significantly suppressed BTMs.1-4,6 A recent phase 3 study evaluating OSP for vaginal dryness found that OSP also dose dependently decreased BTMs,9 similar to results in a phase 2 study.10 The effects of OSP on BTMs were similar to those reported with RLX.10

Conclusions
Studies have demonstrated BTM suppression, BMD increase, and fracture prevention with RLX, BZA, and LAS. Although currently approved to treat menopause-related dyspareunia and vaginal dryness, OSP had beneficial effects on BTMs similar to RLX and may improve the bone health of postmenopausal women when using it to treat vulvovaginal atrophy.

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Topic: 6.9 Selective estrogen receptor modulators SERM's

P305 AYSEX Study: real world data study

observational study, prospective and unicentre to evaluate the improvement of Vulvo Vaginal Atrophy (VVA) in postmenopausal women who receive pharmacological treatment with ospemifene 60 mg/day under conditions

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Objective

The Main Objective is the evaluation of the improvement of VVA in postmenopausal women who receive pharmacological treatment with Ospemifene 60 mg/day under conditions of usual clinical practice after 3 and 12 months of follow-up.
The Secondary Objectives are to evaluate:
- the changes in sexual function,
- satisfaction with the treatment
- endometrial safety
- changes in bone markers
- changes in BMD
- changes in mammography
-Analyze the adverse effects reported throughout the study.
This poster shows the results after 3 months taking ospemifene. In this analysis we evaluate:
Changes in vaginal pH and Vaginal Health, using a vaginal health index Evaluation of the sexual function of women with the FSM Questionnaire. (spanish versión of FSFI)
Evaluation of the improvement of the most bothersome symptoms: (Dyspareunia, vaginal Dryness, Itching and Burning
Evaluate of the quality of life
Study population: 100 postmenopausal women who go to the gynecology service for a review at QuirónSalud San José Hospital and have a diagnosis of VVA will be included. 5 patients left the medication
This poster shows the analysis of the results of 95 patients after 3 months follow-up. These 95 patients had been diagnosed of clinical VVA and they all had a citology with atrophia.
5 patients had suffered breast cancer.

Results

The Vulvo Vaginal Atrophy was evaluated at the baseline visit and at 3 months of treatment. To evaluate it, a Vaginal Health Index was used, ranging from 5(severe atrophy) to 21 (healthy vagina). An statistical ($p<0,001$) and clinical improvement was observed in all aspects evaluated: ph, Epithelial Mucosa, Humidity, Secretion and Elasticity.
Sexual function was assessed with the Women´s Sexual Function questionnaire FSM (Spanish FSFI), at the baseline visit and at 3 months of treatment. Significant improvement was observed in almost all aspects evaluated
The severity of the Most Bothersome Symptoms decreased statistically ($p<0,0001$) and clinically after 3 months of treatment with Ospemifene, mainly dryness and dyspareunia.
The Quality of Life after 3 months of treatment increased from 4.3 to 6.9 points significantly ($p<0,0001$), evaluated with a visual scale.

Conclusions

Patients treated with Ospemifene 60 mg/day for 3 months have demonstrated statistical and clinical significant improvement in VVA: acidification of pH and improvement of MBS, specially in Dyspareunia and dryness. sexual function, and better QoL

Topic: 6.10 Progesterone, progestins SPRM's

P306 The role of progestogen in hypertension in conditions of artificial menopause, *in vitro*

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Recently, *in vitro* we showed that drospirenone improves umbilical artery relaxation, and reduces fibrosis of placental tissue - in samples taken from women with preeclampsia.

Objective

To evaluate effects of drospirenone on blood pressure and morphological changes of myocardium in spontaneously hypertensive rats after ovariectomy.

Material and methods

24 female spontaneously hypertensive rats (SHR) were divided into 3 groups. Group 1 (n=8): ovariectomized rats; group 2: ovariectomized rats treated with Drospirenone; group 3 (n=8) - controls (falsely operated rats). Blood pressure (BP) and histological sections of the myocardium were evaluated.

Results

Significant elevation of BP was found in both groups of animals after ovariectomy when compared to control group: systolic BP was 208±6 mm Hg vs 167±6 mm Hg, $p<0,05$, diastolic BP was 175±8 mm Hg vs 137±8 mm Hg, $p<0,05$. Drospirenone treatment led to significant decrease of both systolic and diastolic BP (to 187±6 mm Hg and 152±6 mm Hg, accordingly, $p<0,05$. We identified metabolic injury and perivascular fibrosis in myocardium after ovariecomy. Drospirenone treatment resulted in a significant decrease of perivascular fibrosis and protected from metabolic damage and myocardium fibrosis.

Conclusion

Ovariectomy leads to further BP elevation in spontaneously hypertensive rats, metabolic injury of myocardium and perivascular fibrosis. Drospirenone intake leads to blood pressure decrease and protects myocardium in the settings of artificial menopause in spontaneously hypertensive rats.

Topic: 6.11 Androgen therapy

P308 Effect of DHEA supplementation on pregnancy rates in egg donation programs in women aged 40 and more

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Context
DHEA supplementation has been reported to have beneficial effects on the IVF/ICSI cycle outcomes of patients with poor ovarian response or diminished ovarian reserve. In several studies was shown direct effect of DHEA on decidualization of endometrium.

Objective
Evaluation of DHEA supplementation on endometrium receptivity for egg donation cycles in patients with advanced age ≥ 40 years.

Methods and Patients
80 women (aged 40-53yy) participating in egg donation program have been investigated. These patients were randomized into 2 groups – I group contained 40 women who received DHEA (25 mg per day) along with conventional protocol during the transfer cycle, II group included 40 women that underwent embryo transfer cycles but did not receive DHEA. All participants undergo egg donation program with good quality one fresh or frozen blastocyst, with normal uterine cavity without or after hysteroscopy. Statistical analysis was conducted by SPSS.21.

Intervention(s)
In both groups donor's stimulation was done with Gonal F in antagonist cycles, with GnRh agonist triggering of final maturation. Fresh donor eggs were fertilized with sperm of partners. ET was done on blastocyst stage. Only cycles with transfer of one good quality non PGT-A blastocysts were included. Kitazato Vitrification-warming media was used.
Endometrium preparation was done with 6 mg oestradiol valerat plus 600 mg vaginal micronized progesterone. ET was done on day 5 plus progesterone start.

Main outcome measures
Biochemical and clinical pregnancy rates, endometrium width during transfer, DHEA-S levels in the blood.

Results
Biochemical pregnancy rates (I group - 80% and II group - 72,5%), as well as clinical pregnancy rates (I group - 62,5% and II group - 57,5%) were higher in I group compared to II group, but difference was not statistically significant. Endometrium width (7,5 ±1,2mm, and 7,8 ±1,4 mm in I and II group respectively) and DHEA-S levels (6,5+/-4,9 ng/ml and 7,5+/-4,1 ng/ml in I and II group respectively) also didn't differ significantly between groups.

Conclusion
DHEA supplementation in upper age patients showed little improvement for biochemical and clinical pregnancy rates although without statistical significance. Further randomized prospective studies are needed to prove the concept.

Topic: 6.11 Androgen therapy

P308b Prevalence of urinary tract infections in women with genitourinary syndrome infections

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Introduction & Objective

Recurrent urinary tract infections (UTIs) are associated with genitourinary syndrome of menopause (GSM) in postmenopausal women. Androgens, in addition to estrogens, have an impact on female genitourinary tissues and may decrease the recurrence risk of UTIs. Vaginal prasterone, an FDA-approved synthetic form of endogenous DHEA, can be converted into active androgens and estrogens. The objectives of this study were 1) to evaluate the prevalence of UTIs in women newly diagnosed with GSM versus women without GSM, and 2) to assess the prevalence of UTIs in women treated with prasterone versus untreated women.

Methods

This was a retrospective cohort analysis using data from Integrated Dataverse database from Symphony Health Solutions collected between 02/2015 and 06/2019. Data was analyzed from women at least 45 years old and who have at least one year of clinical data before and after their index dates. For objective 1, index dates were defined as the first observed GSM diagnosis for the GSM cohort and as a randomly selected outpatient visit date for women without a GSM diagnosis. For objective 2, index dates were defined as the first prasterone fill date for treated women and as the initial GSM diagnosis date for untreated women. To ensure women had a balanced UTI risk profile, women treated with prasterone were matched to untreated women based on age, region, diabetes history, and number of UTI episodes in the year prior to the index date. The UTI prevalence was measured over a 1-year period after the index date. The differential prevalence was assessed using risk ratios (RR).

Results

The prevalence of UTIs was threefold higher (RR 3.0, 95%CI 2.97-3.04) in women diagnosed with GSM compared to matched controls (N=413,207). Women with untreated GSM (N=5,813) had an increased frequency of UTI episodes in the 12 months following the first observed GSM diagnosis ($p<0.05$) compared to their baseline. When compared to women with untreated GSM, women treated with prasterone had a significantly lower UTI prevalence within 12 months of the first prescription fill (RR 0.62, 95% CI (0.56 - 0.68), $p<0.05$).

Conclusions

Women newly diagnosed with GSM have a higher rate of UTIs compared to women without GSM. Results also suggest that the use of prasterone in women diagnosed with GSM may reduce the recurrence of UTIs.

Topic: 6.13 Non-hormonal treatments for climacteric women

P309 Hyalo Gyn gel for the treatment of vulvo-vaginal atrophy in post-menopausal women: a prospective, randomized clinical study

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Context

Vulvovaginal atrophy (VVA) is a distressing medical condition occurring in about 50% of postmenopausal women. Vaginal lubricants and moisturizers are considered first-line therapies for VVA as they hydrate the vaginal mucosa increasing elasticity and softness. Hyaluronic acid (HA)-based moisturizers have been demonstrated to be effective in treating vaginal dryness and irritation.

Objective

To evaluate the efficacy of a HA-based gel, Hyalo Gyn, on improving the perception of vulvovaginal dryness associated with VVA in postmenopausal women after 3 months of treatment compared to no treatment.

Methods

Enrolled patients were evaluated at baseline and at 1 and 3 months.

Patients

Eighty post-menopausal women with VVA were randomized to either the treatment (n=46, mean age 56.7 ± 6.09 yrs) or no treatment group (n=34, mean age 60.1 ± 8.34 yrs).

Intervention

Patients in the treatment group applied Hyalo Gyn gel with a prefilled applicator once every 3 days up to 3 months. Subjects of both groups were allowed to use other lubricants if necessary (not containing HA, hormones or isoflavones).

Main outcome measures

Primary outcome: Verbal Rating Scale (VRS) dryness score at 3 months. Other outcomes: 1) Vaginal Health Index (VHI); 2) VRS median global score change; 3) vaginal pH.

Results

A significant difference compared to no treatment was observed at 3 months in the actual VRS dryness score change from baseline (p=0.0072, Fisher's exact test). Other outcomes, treatment group vs no treatment: 1) VHI median change (min, max): 3.0 (1.0,7.0) vs 1.0 (0.0, 5.0) at month 1 and 4.5 (-1.0, 9.0) vs 1.0 (-2.0, 5.0) at month 3 (p<0.0001 at both time-points, Kruskal-Wallis test); 2) median VRS global change (min, max): -3.0 (-6.0, -1.0) vs -2.0 (-5.0, 0.0) at month 1 (p=0.0015, Kruskal-Wallis test) and -4.0 (-8.0, 0.0) vs -2.0 (-8.0, 0.0) at month 3 (p=0.0006, Kruskal-Wallis test); 3) Vaginal pH improvement: 43.5 % vs 5.9% at month 1 (p=0.0002, Fisher's exact test), 52.2 % vs 8.8% at month 3 (p= 0.0002, Fisher's exact test).

Conclusions

A 3-month treatment with Hyalo Gyn Gel is effective, safe and well-tolerated as it relieves both subjective and objective symptoms of VVA in post-menopausal women.

Topic: 6.14 Sexual health and dysfunction

P310 Investigation on female sexual dysfunction in different stages of reproductive aging in outpatient clinic

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Objective

To investigate the prevalence of Female sexual dysfunction (FSD) in our outpatient clinic for different stages of reproductive aging and to assess the relationship between sex hormones and FSD.

Methods

151 women aged between 40 and 65, without using hormone therapy, were divided according to the stages of reproductive aging into three groups, reproductive group (R), menopausal transition group (MT), postmenopause group (P). Female Sexual Function Index (FSFI) was used for assessing FSD. Estradiol, total testosterone (TT) and free testosterone (FT) were measured.

Results

The prevalence of FSD in R, MT and P were 28.6% (8/28), 47.1% (33/70) and 62.3% (33/53), respectively. The differences between the groups were significant ($x2 = 9.100$, $P = 0.011$). Among postmenopausal women, the prevalence of domain specific sexual problems were 67.9% (36/53) for sexual desire disorders, 32.1% (17/53) for vaginal lubrication disorders, 47.2% (25/53) for orgasm disorders and 58.5% (31/53) for sexual pain. Those sexual problems were significantly higher than those of women in reproductive group and menopausal transition group ($x2 = 8.655$, $P = 0.013$; $x2 = 7.325$, $P = 0.026$; $x2 = 5.411$, $P = 0.0025$; $x2 = 15.835$, $P = 0.000$). FT was significantly lower in women with FSD than that in women without FSD in R (3.00 ± 1.59 pg/ml, 4.48 ± 3.56 pg/ml, $t = 9.385$, $P = 0.006$). Estradiol was significantly lower in women with FSD than that in women without FSD in P (27.62 ± 24.00 pg/ml, 50.95 ± 59.00 pg/ml, $t = 9.082$, $P = 0.005$).

Conclusion

During the three female reproductive aging stages, investigated in this study, the prevalence of female sexual dysfunction gradually increased. Sexual desire disorder, vaginal lubrication disorder, orgasm disorder and sexual pain are the most obvious FSD dimensions in postmenopausal women. FSD was significantly related to the decrease of free testosterone in reproductive women and significantly related to the decrease of estradiol in postmenopause women.

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Funding: Beijing Municipal Administration of Hospitals' Ascent Plan, code: DFL20181401; National Natural Science Foundation of China (81671411); The first batch of Beijing maternal and child health specialist demonstration units "menopausal health specialist" (2018/01-2020/12)

Topic: 6.14 Sexual health and dysfunction

P310b 0.005% estriol vaginal gel improves sexual function in postmenopausal women with vulvovaginal atrophy

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Context

Sexually active postmenopausal women are likely to develop genitourinary syndrome of menopause (GSM), with symptoms that may negatively influence sexual function leading to impairment on self-esteem, loss of intimacy, detraction from enjoyment of sex and consequences on their lives as couples. An appropriate treatment of GSM may be beneficial in the approach of these problems.

Objective

To evaluate the early effect of 50 μg estriol vaginal gel on sexually related symptoms in postmenopausal women with vulvovaginal atrophy (VVA).

Methods

A prospective multicenter study was performed in postmenopausal women with moderate to severe (M-S) symptoms of VVA. 34 women received 1g of 0,005% estriol vaginal gel daily for 2 weeks (w). Symptoms (such as dyspareunia and lack of lubrication) and signs (such as fragility), scored from 0 (absent) to 3 (severe), were reported daily by patients and weekly by physicians. Patient´s perception on sexual intimacy was surveyed at the end of treatment. t-Student and Wilcoxon tests were used for significance analysis.

Results

89% sexually active women reported dyspareunia at baseline (bs), M-S in 83% of them. At the end of study, nearly all women (93%) reported mild or no dyspareunia, in most women (71%) this symptom was absent. Dyspareunia significantly decreased over treatment, reducing 1.1 and 1,8 points after 1w and 2w, respectively (2.1 and 3 points in women that referred dyspareunia as most bothering symptom). Lubrication, present in all women at bs (88% M-S), also progressively and significantly improved over treatment; 35% and 71% women referred absence of lubrication problems after 1 and 2w, respectively. Fragility of the vaginal mucosa, an important cause of bleeding during intercourse, exhibited the most notable improvement among signs: 80% women presented M-S fragility at bs, while it was mild or absent in 70% after treatment (32% with no fragility). By the end of the study 67% women considered their sexual intimacy had improved; a majority (55%) referring this after first w of treatment.

Conclusions

50 μg estriol vaginal gel has proved beneficial in improving sexual health of women with VVA. In addition to its well-known healing effect over the atrophic mucosa, it has shown to significantly and rapidly improve bothersome lubrication problems and pain during intercourse that frequently occur in these women. Moreover, a positive impact on their sexual lives has been perceived as a consequence of treatment.

Topic: 6.16 Plant extracts and steroid receptors

P311 Does black cohosh affect systemic estrogen levels in postmenopausal women?

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Context

Menopause is associated with the onset of major health problems and vasomotor symptoms occurring in 80% of peri and postmenopausal women. Although hormone replacement therapy (HRT) has been considered the standard treatment for all menopause-associated health problems, its use has declined dramatically in the past decade after premature termination of the Women's Health Initiative trial. As a substitute, phytochemicals are increasingly offered to alleviate symptoms associated with menopause. For example, black cohosh root extracts (Remifemin®, Klymadinon®) are widely available. While red clover and soy extracts have been intensively investigated, less is known about black cohosh extracts. The aim of our study is thus to evaluate systemic effects of black cohosh extracts by determining concentrations of estrogens and estrogen metabolites in blood samples from postmenopausal women before and after treatment.

Methods

With the approval of the Medical Ethics Committees, we started a pilot study which includes postmenopausal women before and after taking black cohosh extracts.

The collected serum samples will be analyzed for levels of follicle-stimulating hormone to confirm menopause and for concentration of 27 steroids mainly estrogens and catechol estrogens, but also adrenal precursors and androgens using validated methods. Gas-chromatography coupled to mass spectrometry (MS) will be used to quantify levels of DHEA, androsterone, androstenedione, testosterone, dihydrotestosterone, estrone and estradiol, while liquid chromatography tandem MS will be used for conjugated steroids, sulfates and glucuronides and for measuring 14 catechol estrogens.

Results

Blood samples were taken before and after 2-3 month treatment with Remifemin® following a strict standard operating procedure for sample collection, processing and storage. All relevant clinical and life style data and information about menopausal symptoms of the enrolled women were gathered using validated questionnaires.

Conclusion

To the best of our knowledge this is the first study that will examine the potential systemic effects of black cohosh extracts on the concentrations of steroid precursors, estrogens and estrogen metabolites in blood samples of postmenopausal women. We expect that the results of our study may reveal preventive or promoting effects of these extracts for development of hormone dependent diseases.

The project is funded by the Slovenian Research Agency grant J3-8212 to T.L.R.

Topic: 6.16 Plant extracts and steroid receptors

P312 The Acute Cystitis Symptom Score (ACSS) Italian version as a new tool for diagnosis and follow up of uncomplicated cystitis in female patients

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Introduction And Aim Of The Study

The Acute Cystitis Symptom Score (ACSS) is an 18-item self-reporting questionnaire useful in diagnosis and follow-up of acute uncomplicated cystitis in female patients. Originally developed in Uzbek and Russian language, it is now translated and validated in different languages (www.acss.world).

Purpose of the present study was the linguistic and clinical validation of the ACSS Italian version.

Material And Methods

Translation process was performed using the validated UK-English version of the ACSS as source. The linguistic validation was carried out according to Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments guidelines. Clinical validation was carried out enrolling one hundred Italian speaking women, aged 18 and older. The questionnaire was administered to the patients during medical visit; urinalysis and urine culture were also performed.

Results

Fifty-two women, median age 36 (IQR 28 – 49) were diagnosed with acute cystitis, while forty-eight women, median age 38 (IQR 29 – 45) were enrolled as controls.

Statistical analysis showed good results regarding internal reliability and validity. Mann-Whitney's U test and t-test were used to compare the scores of the groups. ROC curve analysis performed on the six symptoms of the ACSS typical domain cut-off summary score of 5.5 presented a sensitivity of 94% and specificity of 98%.

Most commonly isolated pathogens were Escherichia coli (40 patients), Enterococcus faecalis (7) and Staphylococcus saprophyticus (3).

Conclusions

ACSS has demonstrated to be a simple, reliable and affordable tool that can be used in many different settings, included general medical practice and epidemiological research. Italian version of ACSS has shown to have equal validity compared to the others language versions.

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Topic: 7.1 Genes and gynecological cancers

P315 The effects of Cimicifuga racemosa extract on expression of genes encoding E1-S transporters, estrogen biosynthetic and metabolic enzymes in endometrial and ovarian cell lines

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Context

In postmenopausal women estrogen levels depend exclusively upon the local formation from steroid precursors dehydroepiandrosterone-sulfate and estrone-sulfate (E1-S). The reduced estrogen levels are associated with menopausal symptoms, which often occur in peri- and postmenopausal patients. To mitigate these symptoms nowadays more women choose medicine of natural origin, e.g. extracts from Cimicifuga racemose (CE) instead of hormone replacement therapy, which is associated with increased risk of breast cancer, stroke and pulmonary embolism. While CE treatment is considered as safe, little is known about its effects on healthy endometrial or ovarian tissue and even less on hormone-dependent malignancies like endometrial and ovarian cancer that arise in this population of women.

Object

To examine the influence of CE on the expression of genes encoding E1-S transporters and estrogen biosynthetic and metabolic enzymes in control and cancerous endometrial and ovarian cell lines (CL).

Methods

Control endometrial cell line (HIEEC), ovarian cell line (HIO80) and cell lines of endometrial carcinoma (KLE, RL95-2) and ovarian carcinoma (COV362, Kuramochi) were exposed to CE. The median lethal dose (LD50) was determined and the expression of 9 E1-S transporter genes and 6 genes encoding estrogen biosynthetic/metabolic enzymes were measured using RT-qPCR.

Results and discussion

LD50 for CE in individual cell lines ranged between 107-347 μg/ml. Our results revealed that CE affects the expression of genes encoding E1-S transporters and estrogen biosynthetic and metabolic enzymes in endometrial KLE and ovarian cancer COV362 and Kuramochi CLs, but not in the endometrial CL RL-95-2 and in both control CLs HIEEC and HIO80. In KLE and COV362 there was a significant difference in expression of genes encoding E1-S transporters SLCO4A1 and SLC10A6. In cell lines KLE, COV362 and Kuramochi expression of genes encoding estrogen biosynthetic and metabolic enzymes STS, SULT1E1, HSD17B2 and estrogen receptors ESR1 and ESR2 was significantly changed.

Conclusions

Our research presents an insight of CE effects on endometrial or ovarian cancer CLs at the mRNA level. The effects at the protein level and the level of E1-S metabolism still need to be evaluated.

**Author 1 and 2 contributed equally.*

Topic: 7.2 Hormones and gynecological cancers

P315b Studies of estrogen formation in model cell lines of ovarian and endometrial cancer

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Context
Ovarian (OC) and endometrial (EC) cancers are generally considered as post-menopausal, hormone-dependent pathologies with increasing incidence and mortality rate. Estrogen intracrine action is considered vital in the cancer initiation and progression. Estrogens can form locally from androgen and estrogen precursors, through the aromatase and sulfatase pathway, respectively.

Objective
To assess whether the sulfatase pathway contributes to the formation of active estrogens in model cell lines of OC and EC by means of LC-MS/MS.

Methods
Control and model cell lines of high-grade serous OC and moderately differentiated EC were incubated with 2.3, 8.5, and 85 nM estrone sulfate (E1-S) for 8, 24, 48 and 72h. After each incubation time point, the cell culture media was collected, the estrogens of interest extracted by solid phase extraction, and the samples were subjected to an LC-MS/MS. The quantification of the data was performed using the internal standard approach and standard calibration curves.

Results
The sulfatase pathway is active in both, control and model cell lines of OC and EC. Interestingly, the overall estrogen change upon incubation with the estrogen precursor differs between OC and EC model and control cell lines, and this difference intensifies as the E1-S concentration increases. More specifically, E1-S is metabolized to estrone (E1), and this transformation happens significantly faster in OC and EC cell lines, eventually leading to a significantly higher E1 levels in the OC and EC cell lines comparing to their respective control. The subsequent E1 reduction leads to estradiol (E2) formation, which is altogether higher in the OC and EC cell lines than in their control line. The changes in the sulfated product of E2 are minimal in both control and model cell lines.

Conclusions
The sulfatase pathway is active in the control and OC and EC model cell lines, nonetheless its contribution to active estrogen formation is significantly greater in the OC and EC model cell lines than in their control cell line. We suggest that the higher levels of active estrogens present in the cancerous cell lines have a role in OC and EC initiation and progression, acting as pro-proliferative hormones, as well as a genotoxic agents following oxidative transformation.

Topic: 7.2 Hormones and gynecological cancers

P317 Juvenile granulosa cell tumor: a case report of 16 years-old female with adnexial mass

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Context

Ovarian tumors are important childhood neoplasms make up to 1.5 % of all childhood malignancies. The most frequent malignant tumor in girls and adolescence is the germ cell tumors with percentage of 35 to 45.

Case

In this case; a 16 years old female with lower abdominal pain, nausea found to had a 98*65 mm hypoechoic mass in her right ovary. As laboratory, all tumor markers including CA 125 and hormonal profile were normal, only Anti-Müllerian hormone (AMH) was 23 (normal range 0.05 – 11), Beta human chorionic gonadotropin(B-HCG) was 0.01 (negative), Lactate Dehydrogenase was 178 (normal <600). She was underwent laparoscopic cystectomy of a 90*70 mm adnexial mass. Histopathological examination reported a granulosa cell tumor on right ovary. On immunohistochemical evaluation, the ovarian mass was positive for Inhibin. Calretinin was focally positive, and it was negative for pancytoceratin and hence the diagnosis of juvenile granulosa cell tumor was confirmed. A second surgery was planned for the staging: right salpingoophorectomy, left ovarian biopsy, omentectomy performed laparoscopically. Histopathology showed that 0.6 cm residual mass of granulosa cell tumor was seen at right salpingoophorectomy material. The specimens from omentum and the left ovarian biopsy were resulted as benign.

Discussion

Granulosa cell tumors are the most common type of ovarian sex cord-stromal tumor; they comprise 2 to 5 % of all ovarian malignancies. There are two subtypes of this tumors: adult&juvenile types. For diagnosis, immunohistochemical staining (IHC) is important for these group of tumors. Inhibin is the most sensitive and specific stain. In this case, the staining of the tumor was positive for inhibin and Calretinin. For the laboratory, only AMH level were high. The most common complaint of patients on admission is abdominal pain and abnormal vaginal bleeding. The granulosa cell tumors usually secrete estrogen and progesterone, which may cause hyperestrogenism symptoms. In our case, patient had none of these symptoms except for the abdominal pain.

Conclusion

Patients within adolescence age group should be evaluated carefully; even though all tumor markers are negative, the recommended treatment option for those patients are surgery. Recommended surgery for patients who completed childbearing is a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Adjuvant chemotherapy is usually required for patients who have stage 2-4 granulosa cell tumors.

Topic: 7.5 Screenings and for gynecological cancers

P318 Adherence to treatment among patient with cervical intraepithelial neoplasia

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Objective
The aim of this study is to evaluate the compliance of patients to management recommendations for CIN 2 or 3 and to determine factors contributing to non compliance of these patients.

Method
This retrospective study analyzed all medical records of patients who had been diagnosed with CIN 2 or CIN 3 from January 2013 until December 2015 in University Kebangsaan Malaysia Medical Centre (UKMMC). The diagnosis of CIN 2 or CIN 3, demographic data and the compliance to the treatment and follow up given were recorded. The reason of the non- compliance was assessed via phone after verbal consent obtained.

Results
There were 40 patients who were newly diagnosed with CIN 2 or CIN 3 in between 1st January 2013 to 31st December 2015. 65 % of the women were compliance to the recommended management. However, there were 35% of women who had declined the treatment and defaulted the follow up. The main reason of the non compliance was due to patients were already moved out to other states.

Conclusion
Patients were overall highly adhered to recommended management when diagnosed with CIN 2 or CIN 3. No predictive factors identified for non adherence.

Topic: 7.5 Screenings and for gynecological cancers

P319 Asymptomatic postmenopausal women: what are the risk factors for endometrial malignancies? A retrospective multicentric study

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Context

Endometrial cancer is the most common gynecological neoplasia in developed countries. Its incidence is increasing, due to population aging and obesity growth, its main risk factors. Despite this, there is no indication of population screening because its mortality rate does not change. In this way, the diagnosis of endometrial malignancies comes from the investigation of symptomatic women, that is, women with postmenopausal bleeding. However, in asymptomatic women, there are questionings if systematic endometrial evaluation would benefit the population in question by the earlier diagnosis or if it would result in unnecessary interventions.

Objective

To evaluate the prevalence and risk factors for endometrial malignancies in asymptomatic postmenopausal women.

Methods

Multicentric retrospective study.

Patients

1003 asymptomatic postmenopausal women. Intervention: All the asymptomatic postmenopausal women who were submitted to hysteroscopy with biopsy in University of Campinas and Pérola Byington Hospital were included. Excluded women with postmenopausal bleeding, without anatomopathological results and whose medical records were not complete.

Main outcome measure

The variables analyzed were age; parity; body mass index; duration of menopausal status; systemic arterial hypertension; diabetes mellitus; use of hormone replacement therapy; use of tamoxifen; duration of use of tamoxifen; endometrial thickness and endometrial malignancies (atypical endometrial hyperplasia and endometrial cancer).

Results

The frequency of endometrial malignancies in asymptomatic postmenopausal women was 2.39%. The mean age of asymptomatic postmenopausal women without endometrial malignancies was 60.75 ± 9.63 years, compared with 61.92 ± 7.84 years of those with these affections (p=0.516). The group without malignancies had a mean body mass index of 29.03 ± 5.64 kg/m^2. Whereas the other group had an index of 29.32 ± 5.22 kg/m^2 (p=0.715). Endometrial thickness ≥ 8 mm increased the chance of endometrial malignancies, even more, with an endometrial thickness ≥ 12.55 mm the chance of endometrial malignancies increased by 4.68 times (p <0.001 and 95% CI: 1.99-11.03).

Conclusions

The prevalence of endometrial malignancies was low and the only risk factor for endometrial malignancies in asymptomatic postmenopausal women was endometrial thickness.

Keywords: endometrial thickness; transvaginal ultrasound; hysteroscopy; risk factors; endometrial cancer.

Topic: 7.5 Screenings and for gynecological cancers

P320 BioEndoCar: in search of new biomarkers for diagnosis and prognosis of endometrial carcinoma

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Context

Endometrial carcinoma (EC) is the most frequent gynecological malignancy in the developed world. Currently there are no valid non-invasive diagnostic or prognostic methods available and therefore, diagnosis and treatment of EC patients is guided by histopathological and surgical findings. The lack of non-invasive diagnostic and prognostic biomarkers of EC is addressed in the current clinical study titled "Biomarkers for Diagnosis and Prognosis of Endometrial Carcinoma" (BioEndoCar).

Methods

Prospective observational case – control study. Patient recruitment takes place at three medical centers (University Medical Centre Ljubljana, Slovenia; Maastricht University, The Netherlands; Lublin Medical University, Poland). Plasma samples from women with diagnosed EC and controls will be examined using non-targeted and targeted metabolomics (Helmholtz Zentrum München, Germany) and semi-targeted proteomics approaches (Sciomics GmbH, Heidelberg, Germany). Combined blood metabolome (>850 metabolites), proteome (>900 proteins), clinical and epidemiological data will be analyzed (University of Tartu, Estonia) in order to construct diagnostic/prognostic algorithms for early diagnosis of EC and to identify patients with low/high risk for cancer progression and recurrence.

Results

BioEndoCar project has defined inclusion/exclusion criteria and a strict standard operating procedure for sample collection, processing and sample storage that is followed in all three medical centers. Since the beginning of the project (April 1st, 2018) we recruited more than 200 patients in total. Discovery proteomics analysis is currently in progress (Sciomics GmbH, Heidelberg, Germany) and we are awaiting the results. Great effort was put into informing the lay and expert public about the importance of the translational studies in EC. BioEndoCar project has been presented at the ENITEC meeting and the ESGO congress. We have established an official website (https://bioendocar.eu/), Twitter profile and Facebook page (https://www.facebook.com/bioendocar) where we post all news concerning the project.

Conclusion

Within the project we expect to find different metabolic and protein profiles in patients with early stages of EC as compared to controls and in patients with poor prognosis with high risk of disease progression and recurrence as compared to those with favorable prognosis.

Funded by ERA-NET Transcan2.

Topic: 7.5 Screenings and for gynecological cancers

P321 Efficacy on cytological findings. i.e. ASC-US, LSIL, ASC-H, and HSIL of an environment modifying vaginal gel – novel management for the prevention of cervical cancer: a subanalysis of a randomized controlled trial

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Objectives

There is yet no single validated non-surgical therapeutic approach for mild to moderate cytopathological findings. The present clinical trial aimed to study the effect of such a treatment with SAM vaginal gel. SAM vaginal gel is a medical device containing adsorptive silicon dioxide and an antioxidative citric acid / selenium combination.

Material and methods

216 women aged 25-60 years participated in this study at three colposcopy centres. They were randomised to either receive an intravaginal daily dose of SAM gel for three 28-days periods, or be followed-up clinically without intervention, corresponding to gynaecological guidelines,.

The outcome was cytological efficacy, analysed as regression, remission, persistence and progression. At baseline, all participants had colposcopy-guided biopsies. At 3 months, they had a cervical smear for cytology, hr-HPV and p16/Ki-67 (CINtec® Plus) test; at 6 months, they had a cervical smear for cytology and p16/Ki-67 (CINtec® Plus) test only.

Results

Regression of cytopathological findings at 3 months, were observed in 77 out of 108 patients (71.3%) in the SAM gel arm, whereas a similar finding was seen only in 27 out of 108 (25.0%) in the control arm. The combination of regression and progression of cytopathological findings was in favour of patients treated with SAM gel at 3 months in the low risk and in the high-risk group and sustained at 6 months.

Conclusions

SAM vaginal gel enhances regression with a significantly decreased progression rate (6.5%) compared to the strategy of 'watchful waiting' (18.5%) over a period of 3 months in cytopathological findings, thus offering an active management to prevent cervical cancer.

Topic: 7.5 Screenings and for gynecological cancers

P322 Surface CD200 and CD200R antigens on lymphocytes in endometrial cancer

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Introduction

Endometrial cancer (EC) is one of the leading causes of female cancer death worldwide. The membrane glycoprotein CD200, widely expressed on multiple cells/tissues, uses a structurally similar receptor (CD200R), delivering immunoregulatory signals. There is an evidence that CD200/CD200R signaling suppresses anti-tumor responses in different types of malignancies. Little is known about CD200/CD200R pathway in EC. The aim of the study was to evaluate the frequencies of CD200+ and CD200R+ lymphocytes in patients with EC.

Material and methods

Twenty female patients primarily diagnosed with EC and twenty age- and sex-matched healthy persons were enrolled. The viable peripheral blood lymphocytes underwent labeling with fluorochrome-conjugated monoclonal antibodies, and were analyzed using a flow cytometer.

Results

In EC group, the percentages of T CD3+/CD4+ and T CD3+/CD8+ cells expressing CD200 antigen were higher than in controls ($p<0.0001$). In EC group, the frequencies of T CD3+/CD4+ and T CD3+/CD8+ cells expressing CD200R were lower than in controls ($p<0.001$, $p<0.004$, and $p<0.002$, respectively). The percentage of B CD19+/CD200+ lymphocytes was higher in EC patients than in controls ($p<0.00001$). Lower frequency of B CD19+/CD200R+ cells was observed in EC patients comparing to controls ($p<0.00001$). The differences in the frequencies of CD200+ and CD200R+ lymphocytes were found in relation to histological grading of the tumors.

Conclusions

Deregulation of CD200/CD200R axis is important for EC pathogenesis. High percentages of lymphocytes with CD200 expression may contribute to the continuous T cells activation, development of chronic inflammation and influence endometrial carcinogenesis.

Topic: 7.5 Screenings and for gynecological cancers

P322b The logistic regression model with HD-flow analysis for preoperative diagnosis of ovarian tumors

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Aim

The idea behind the development of predictive models for a differential diagnosis of ovarian tumors (DDOT) is to enable inexperienced sonographers to undertake diagnoses. The aim of this study was to develop predictive model based on HD-flow analysis - the novel tool for the evaluation of tumor vasculature.

Methods

The study group included 94 malignant and 50 benign patients diagnosed in Private Medical Practice Dariusz Szpurek due to ovarian tumor. The patients underwent ultrasound examination according to the International Ovarian Tumor Analysis (IOTA) group guidelines. We developed the logistic regression model (LR) to distinguish benign from malignant ovarian tumors. The model was further validated prospectively on the group of 35 benign and 25 malignant ovarian tumor patients.

Results

We identified the following variables as predictors of malignancy: age > 50; CA125 > 85 U/ml; HD-flow score ≥ 3; tumor dimension > 90 mm; presence of solid elements. However, the LR model included only 3 independent variables: HD-flow score (with coefficient 2.11), tumor dimension (1.43) and the presence of solid elements (2.21). The intercept was equal to-1.34.The best cut-off value was the 0.14. In the development date set the LR model achieved sensitivity, specificity, positive and negative likelihood ratio of: 72%, 87%, 5.5 and 0.32, respectively; while, in the validation group: 64%, 83%, 2.45 and 0.24.

Conclusions

The analysis of tumor vasculature by HD-flow technique is a useful for development of prognostic models for DDOT.

Topic: 7.6 HPV and HPV vaccines

P324 Colposcopy and microscopic modifications in cervical lesions associated with HPV 16 and 18

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Introduction

The are many strains of Human Papilomavirus (HPV) and 14 of these have been asociated with cervical cancer. Two strains, 16 and 18, are responsible for 70% of the pre-neoplasic lesions and cervical cancers. Precancerous cervical lesions can be treated and the HPV infection can clear itself out under the influence of the immune sistem in 4 months up to 2 years. Persistant infections can transform a normal cervix into a pathologycal one.

Materials, methods and resault

A 28 years old patient presented in the Ambulatory Service accusing vaginal bleeding in small ammount after intercourse. During the speculum examination, the cervix was enlarged and presented a lesion area which bled upon spontanously. PAP smear was performed which revealed abnormal scuamos cells (ASCUS) and at the HPV blood test the presence of 16 and 18 HPV strains was found. Colposcopy with cervical biopsy was performed. The resault identified CIN 1, 2 and 3 is some areas and conisation was performed afterwards. He fragment underwent microscopical study. With the aid of immunohistology we demonstrated the presence of HPV in the tissue (positive reaction with the anti-HPV antibodies, anti-p16), high proliferative intraepithelial grade (CIN 1- postive for anti-Ki67 antibody in the basal layer, CIN 2- positive reaction in the basal and intermediate layers, CIN 3- positive reaction in the basal, intermediate and superficial layer. We also had positive reaction for some cells which underwent cell division with the anti tumoral protein 53 (p53).

Conclusions

HPV infection can influence normal cervical cell transforming them into pre cancerous or malignant cells. Early detection and treatment of these modifications can stop the pathological evolution and reduce the number of high stages and untreatable cancers.

Topic: 7.7 Border-line and pre-tumoral lesions

P325 Endometriosis in the caesarian section scar as a substratum of aggressive malignant tumour

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Context

Malignant transformation in the endometriotic lesions is a well-known phenomenon; however, most of the cases include the transformation of ovarian endometrioma to ovarian cancer. Other locations are very rare. It is estimated that ovarian endometrioma increases the risk of ovarian cancer 2-3 times.

Objective

A clinical case of a 60-year old female with a neoplastic transformation of the endometrioid tumor at her cesarean section scar is presented.

Result(s)

The patient presented to the Oncology clinic after initial surgery in the regional hospital. She had undergone a Cesarean section once 20 years ago and had no relevant medical history. At the clinical onset of disease, the nodule grew quickly to a large size with no significant pain. Physical examination revealed a smooth mass measuring 10 to 12 cm in diameter which was bleeding and disintegrating. A biopsy of the mass showed clear cells and necrosis. Magnetic resonance imaging (MRI) revealed muscle infiltration, solid-cystic consistency, without peritoneum and bladder infiltration. She was disqualified from radical resection and qualified for chemotherapy treatment with carboplatin. Because of bleeding the tumor was dissected at the regional emergency surgery unit with adequate margin. Local lymph nodes biopsy showed metastases. Histopathological examination showed the lesion to be clear cell adenocarcinoma. After two months the patient was hospitalized due to suspicion of the kidney's angiomyolipoma and histopathological examination showed the lesion to also be clear cell adenocarcinoma with the point of origin in reproductive organs. The PET scan showed active metastases in both of the lungs, iliac and inguinal lymph nodes. The patient died due to thromboembolism in a course of disseminated disease.

Conclusions

Clear cell carcinoma arising on the basis of the endometriotic tumor is an extremely aggressive and rare tumor. However, an increasing number of Cesarean sections will lead to more cases in the near future. Rough estimations from literature show that 1 in 100 women after the Cesarean section will develop endometriosis in a scar, and approx. 1 in 100 cases of scar endometriosis will be complicated by a malignancy. The management is not well established and there are no relevant data on prophylaxis of the tumor. More cases are needed to elucidate the clinical management of this disease but careful screening in women that underwent the Cesarean section should be considered.

Topic: 7.9 Conservative approaches to gynecological cancers

P326 Successful conservative treatment of early stage endometrial cancer 22 y.o. women with Turner's Syndrome

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Endometrial cancer and conservative treatment this disorders in patients with Turner's syndrome (TS) have very rarely been reported. We present rather rare case of early stage diagnosed and successfully cured endometrial cancer in 22 y.o. Turner's Syndrome woman. Young 22 y.o. woman came to gynecologist because of menstrual irregularities and need for contraceptive advice. She has spontaneous puberty and menstrual function. Some dysembryogenetic stigmas made us referred her to genetics for blood karyotype investigation. Mosaic blood lymphocytes karyotype 45X 83 %/46XX 17% was discovered. Transvaginal ultrasound examination found the endometrial abnormalities such as irregular thickness. Following endometrial Pipel-biopsy showed foci of atypical hyperplasia and patient was referred to the hysteroscopy, where was founded local lesions and hysteroscopic focal resection and random biopsy was performed. Pathological examination founded atypical endometrial hyperplasia associated with high grade endometrioid adenocarcinoma G1. Pelvics MRI didn't find any abnormalities like endometrial invasion ore lymph-nodes involvement, laparoscopy didn't find ovaries involvement, colonoscopy was normal. We investigated ovarian reserve and found normal range of FSH, not extremely low AMH (0,6 ng/ml), primordial and dominant follicles in her ovaries. Ex concilium and after informing the patient we made decision about fertility preservation treatment. Megestrol acetate 160 mg daily was prescribed. Three months after start of hormonal treatments control hysteroscopy with endometrial biopsy has done. Pathological examination found atrophic and decidual endometrium and megestrol acetate 160 mg was continued. Seven months after start of treatment we did second hysteroscopy with endometrial biopsy and atrophic endometrium was found again. We stopped hormonal treatment and referred patient to reproductologist for embryo cryopreservation (till this time patient got married, but didn't ready to planning pregnancy). Unfortunately, first embryo cryopreservation attempt wasn't successful. Now patient wants to make some break in her medical care and she is taken desogestrel 75 mcg. like contraceptive option. We are planning to make second attempt of embryo cryopreservation in the February 2020. We and patient clearly understand she has little chance for pregnancy, but she and her family decided to use every possible chance.

Topic: 8.1 Breast development and function

P327 Observations on the morphological characteristics of mammary gland growth and supportive tissue in the course of gestation in mice

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Context
Fibrous connective tissue develops in the breast to maintain the structural integrity of the breast. Since it was first described by Astley Baston Cooper, in an 1840 report on the anatomy of the human breast, this fibrous connective tissue has commonly been referred to as Cooper's ligaments. However, Cooper's ligaments are described differently, depending on the anatomy textbook and the literature, which makes it difficult to fully understand this structure.

Objective
The objective of this study was to obtain anatomical insights by observing mammary gland development and associated histological changes around the mammary gland in deep layers of subcutaneous tissue in mice from gestation through nursing.

Methods
One by one, pieces of tissue were isolated from around the mouse teat, fixed, dehydrated, cleared with xylene, then infiltrated with paraffin. Tissue pieces were then embedded in paraffin, a series of successive sections was prepared from the tissue block, and after deparaffinization, the sections were observed under an optical microscope following hematoxylin and eosin (HE) staining and trichrome staining.

Results
In mice, subcutaneous tissues were divided into two layers by a layer of muscle called the panniculus carnosus that develops with age, and mammary glands were distributed below this layer. In young animals from 3 weeks or 1 month of age, the number of mammary glands increased in number and gradually become more developed with age. In terms of reproductive function, large ducts were observed in 2-month-old mice (equivalent to adulthood in humans) and fibrous tissue connecting these ducts and the developed mammary glands were observed to run through the adipose tissue. The number of lobules and ducts observed in adipose tissue was higher on the day of delivery. After parturition and during nursing, the lobules and ducts were densely arranged, and thick, rounded individual acinar cells were observed. Fibrous tissue was also observed around the mammary glands. In mice that did not nurse, compact and strongly stained cell groups, believed to be the remnants of mammary glands, were observed after parturition. However, even more strongly stained fibrous tissue was also observed in multiple locations, running between the surface adipose tissue and deep layers between these remnant mammary glands. Tissue confirmed to be fibrous tissue by HE staining was shown by trichrome staining to be collagen fiber. This collagen fiber was distributed in a manner that surrounded developed mammary glands.

Conclusions
Fiber structures that surround the mammary gland develop during growth in mice, create a net-like pattern by connecting with collagen fibers that form a deep layer fascia for panniculus carnosus striated muscle, connect to ducts and mammary glands, and are believed to support these structures. After comparing mice that nursed with mice that did not nurse after parturition, we believe the fibrous connective tissue grows to form lobules and supports developed mammary glands that grow to make milk. This fibrous connective tissue is thought to affect mammary gland development more so after parturition than during gestation and strengthens the net-like structure of collagen fiber found within subcutaneous tissue around the mammary gland.

Topic: 8.2 Hormones and the breast

P328 Local and systemic sex hormones concentrations in different subtypes of breast cancer in postmenopausal women

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Context

Nowadays there is a remaining question, why in postmenopausal women, despite the deficiency of estrogen and progesterone without a significant drop in androgen levels, there is a sharp increase in the frequency of hormone-receptor positive breast cancer subtypes. According to some studies, blood estrogen levels might not reflect their actual levels in breast.

Objective

To assess the local concentrations of sex steroids in breast tumor in comparison with surrounding tissue and serum in postmenopausal women with different molecular subtypes of breast cancer.

Material

48 postmenopausal women with different molecular subtypes of breast cancer (luminal A, luminal B, with or without progesterone receptors, triple-negative) and 12 premenopausal women with hormone-receptor positive breast cancer (a comparison group). One sample of tumor and normal tissue of the same breast, as well as serum were examined to determine the levels of key sex hormones.

Methods and measurements

We conducted a cross sectional study: immunohistochemistry and PCR for evaluation of expression of receptors for sex hormones (estrogens, progesterone, androgens) in breast tumor. Levels of a set of steroid hormones in breast tissue and serum were evaluated by liquid chromatography-tandem mass spectrometry. The set included aldosterone, cortisol, corticosterone, 11-deoxycortisol, DHEAS, estradiol, estrone, testosterone, DHEA, 11-deoxycorticosterone, androstene-3,17-dione, 17-α-hydroxyprogesterone, dihydrotestosterone, androsterone, pregnenolone, 17-α-hydroxypregnenolone and progesterone. Preparation for the analysis of all hormones, except estrogens, consisted in extraction with methyl tert-butyl ether. Estrogens were first extracted with methyl tert-butyl ether and the derivatized with dansyl chloride to increase sensitivity of the method. Contents of the steroid hormones in tissues were evaluated semi-quantitatively. The obtained mass spectrometric data were evaluated with Wilcoxon-Mann-Whitney together with PCA and PLS-DA multivariate analysis.

Results and conclusion

We will present the comparative analysis of local concentrations of sex hormones in breast tumor and surrounding tissue in postmenopausal women with breast cancer of different molecular subtypes in comparison with circulating levels of hormones, as well as local expression of receptors for sex hormones.

Topic: 8.4 Breast carcinogenesis

P329 The clinicopathologic patterns of breast tumours in Libyan patients: 9 years' retrospective study

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Context
It is estimated that 6308 cancer cases were registered in the year 2018. Breast cancer is the most frequent cancer constituting 12% of all Libyan cancers in both sexes according to the World Health Organization and International Agency for Research on Cancer a report of Libya.

Objective
We aim to determine the clinicopathological patterns of breast tumours in Libyan patients.

Methods and Patients
This is an observational retrospective study. A total of 996 specimens of breast tissue were collected from different hospitals and clinics in Tripoli. Two histopathologists verified all slides. Statistical analysis and multivariate regression models were done using SPSS 25.

Results
Out of 966 patients identified during nine-year reports. The age range of the cases was 18-80 years with a mean age of 33.69±13.2. The histopathologic pattern of breast tissue was as follows: fibroadenoma 444 (45.9%), breast adenoma 24 (2.4%), ductal papilloma 7 (0.7%), and two phylloid tumours 2(0.2%). Also, fibrocystic breast changes were identified in 295 (30.5%) of the pathological specimen. However, malignant lesions comprised 224 cases, of which; ductal carcinoma 160 (16.5%), medullary 20 (2%), lobular carcinoma 6 (0.62%), and 38 undifferentiated carcinomas.

Conclusion
Fibroadenoma is the most frequent diagnosis among breast specimen, followed by fibrocystic change. Of note, invasive ductal carcinoma was the most prevalent cancer in the diagnosis. In conclusion, breast cancer in Libya has the same pattern and demographics as reported in the recent international literature for the world population as well as for region of the Middle East and North Africa.

Topic: 8.4 Breast carcinogenesis

P330 Bacteria and breast cancer new evidence

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Liberi professionisti

Context

In a newly published study, researchers have uncovered differences in the bacterial composition of breast tissue of healthy women vs. women with breast cancer.
In cancer research, the tumorigenic ability of pathogens is being recognized.
The Human Microbiome Project analyses, by the DNA-RNA sequencing methods, the universe of microbes that live in different habitats of our body.
The largest collection of these microorganisms is found in the gastrointestinal tract. Microbial composition reflects both genetic and lifestyle variables of the host. Microbial perturbation (dysbiosis) could contribute to the risk of developing health problems. Gut microbiota is capable of modulating estrogen serum levels

Objective

In this review, we discuss recent knowledge about the microbiome and breast cancer. Cancer in general is a complex disease, the precise etiology is still unknown, but the combination of genetic, epigenetic, and several environmental and lifestyle factors has been identified and strongly related.
A dysbiotic microbiota might promote malignancy by inducing genetic instability, initiating DNA damage and proliferation of the damaged progeny, alteration of the immune response, metabolic dysregulation, inflammation, higher levels of endogenous estrogens, autoimmune diseases, thyroid dysfunction and altered carbohydrate metabolism.

Methods

To clarify this aspect we investigated 250 patients aged between 30 and 80 years, referred to our clinics they developed breast cancer, with stage I–III, compared with 200 patient without cancer as a control.
Function thyroid, adrenal, pancreas, pituitary gland,ovary were evaluated,
ultrasonogram of the thyroid gland, breast, gut, pancreas, liver, kidney, uterus and ovary was performed on all patients.

Results

In our clinical practice, we have found the possible correlation between gut microbiome alterations to gluten exposure. Gluten appear as a endocrine disruptors and has epigenetic power, therefore it appears to man the greatest suspect in breast cancer process. A mutation affecting a tumor suppressor gene increases the probability of malignant neoplastic processes occurring. Gluten can make these genes defective due to a methylation defect.Our study promote possible key intervention strategies and the role of diet in the development and prevention of DNA damage, growth factors and inflammation in cancer development and progression as well as the role of diet in regulating the human microbiome.

Topic: 8.4 Breast carcinogenesis

P331 Gene expression of kallikreins in normal and malignant breast cell lines

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Context

Kallikreins (KLKs) are secreted serine proteases involved in various physiological and pathological processes. Their expression is regulated predominantly by steroid hormones. KLKs are supposed to be involved in breast cancer (BC) development.

Objective

We analyzed the gene expression of the "classic" KLK1 and all "new" kallikreins (KLK4-KLK15) in relation to the molecular characteristics and *in vitro* invasiveness of 21 malignant and three normal breast-derived cell lines (CLs).

Methods

CLs were cultured in a fibroblast-collagen-based *in vitro* invasiveness assay. Gene expression of KLKs was determined by using real-time polymerase chain reaction and normalized to the expression of housekeeping gene beta-2-microglobulin. Differences in KLK gene expression in relation to androgen (AR), estrogen (ER), progesterone (PR), epidermal growth factor (EGFR), and human epidermal growth factor 2 (HER2) receptors were examined with the Kruskal-Wallis test and Steel-Dwass-Critchlow post hoc procedure. Cluster analysis was performed by generating a heat map. Prediction of *in vitro* CL invasiveness was investigated using logistic regression.

Results

KLK5 and KLK7–KLK11 were downregulated in several BCCLs. In contrast, KLK4, KLK8, KLK12 and KLK15 demonstrated strikingly high expression in two BCCLs, UACC 812 and MDA-MB-330. Significant differences in KLK1 and KLK5–KLK9 gene expression were related to the AR presence, with significantly higher KLK expression observed in AR-negative BCCLs and normal breast CLs. On the contrary, the KLK expression often remained low or absent in AR-positive BCCLs. With regards to the ER, the only significant difference was for KLK9, however KLK7 and KLK8 nearly approached the significance level ($p = 0.053$ for both). Additionally, KLK7 expression differed according to the EGFR expression. Two KLK clusters were identified (first: KLK1,4,12,15; second: all other KLKs), with two subclasses within the second cluster (KLK5–9 and KLK10, KLK11, KLK13, and KLK14). CLs that expressed at least six KLKs belonged predominantly to basal or HER2 intrinsic subtypes. Six out of 21 BCCLs — all of them being negative for AR, ER, and PR — were located close to normal CLs on the heat map. No KLK predicted the *in vitro* invasiveness of CLs.

Conclusions

The gene expression of KLKs is mostly downregulated in BCCLs and often related to the presence of AR. The identified gene expression clusters indicate the functional interplay of selected KLKs in BCCLs.

Topic: 8.5 Hormones, breast cancer proliferation and metastasis

P332 Blood and breast cancer tissue concentrations of PGRMC1 are correlated to tumor growth induced with norethisterone in contrast to neutral progesterone and dydrogesterone

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Objectives

Progesterone receptor membrane component 1 (PGRMC1) is mediating an increase of breast cancer cell proliferation induced by certain synthetic progestogens which we were able to show in a series of already published in-vitro studies. Aim of this research was, using an animal model, to compare tumor growth with progesterone (P) and its isomer dydrogesterone (DYD) with norethisterone (NET), which elicited in in-vitro studies the strongest proliferating effect, and for the first time to investigate if growth can be correlated both with blood and tissue concentrations of PGRMC1 to identify PGRMC1 as possible new tumor marker to predict the risk using menopausal hormone therapy (MHT).

Methods

Prospective, randomized, blinded, placebo-controlled four-arm study (45-50 days); PGRMC1-transfected or empty-vector T47D and MCF7 xenotransplants were each treated with four different hormonal preparations: E2+placebo; E2+dydrogesterone; E2+progesterone; E2+norethisterone. A total of 112 six-week-old castrated BALB/c female mice were randomly allocated to the 16 groups (7/group). Tumor volumes were monitored twice weekly. PGRMC1 was assessed in the blood by a novel ELISA. Tissue expression was assessed by immunochemistry.

Results

In T47D- and MCF7-PGRMC1 xenografts, E2-induced tumor growth increased with norethisterone but not with dydrogesterone or progesterone. Less tumor growth in non-PGRMC1-transfected xenografts, without between-group differences. Blood concentrations as well as tissue expression of PGRMC1 using E2/NET in both PGRMC1-xenograft groups (TD47D and MCF7) were significantly higher than in all the other 14 groups ($p < 0.05$).

Conclusion

In our animal model NET added to E2 increases tumor growth in the xenografts which got transplantation with PGRMC1-transfected TD47- or MCF7 cells, in contrast to progesterone and dydrogesterone which both show similar low proliferative potency. Since in our study using norethisterone the higher PGRMC1 concentrations in blood were associated with greater tumor growth. Clinical studies may be important to investigate if PGRMC1 assessment in blood of breast cancer patients can be predictive for the prognosis of breast cancer patients.

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Funding: National Natural Science Foundation of China (81671411); The first batch of Beijing maternal and child health specialist demonstration units "menopausal health specialist" (2018/01-2020/12)

Topic: 8.5 Hormones, breast cancer proliferation and metastasis

P333 Progesterone receptor membrane component 1 (PGRMC1) promotes the AKT pathway to induce breast cancer cell proliferation

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Objective

We already have published extensively on the effect of PGRMC1 on hormone-induced proliferation of various breast cells demonstrating a strong increase especially with the use of norethisterone (NET). However, until now the mechanisms are not very clear. We describe here how the Casein Kinase 2 (CK2) phosphorylation site Ser181 phosphorylation within the PGRMC1 molecule enables important new insights into the possible regulation of breast cancer cells proliferation.

Methods

PGRMC1-mediated breast cancer cellular proliferation and phosphorylation of PGRMC1 were studied using wild-type (with hemeagglutinin-tagged) MCF-7 cells, which were stably transfected with expression vector containing HA-PGRMC1 (MCF-7/EVC cells), PGRMC1 (MCF-7/PGRMC1 cells) and Ser181 point mutated PGRMC1 (MCF-7/PGRMC1-S181A cells). These three types of MCF-7 cells were stimulated with norethisterone (NET) and estradiol (E2), and thereafter cancer cell proliferation activity and the correlation between PGRMC1 and Akt pathways in malignant proliferation of breast cancer was detected by CCK-8 and immunohistochemistry respectively.

Results

NET and E2 elicited a significant proliferation in MCF-7/EVC at 1μM and 10-10 M, respectively. Compared with MCF-7/EVC, the cell proliferation in the MCF-7/PGRMC1 was significantly accelerated ($p<0.05$). MCF-7/PGRMC1-S181A cells impaired the proliferation during NET/E2 treatment ($p<0.05$). MCF-7/PGRMC1 did increase the phosphorylation of AKT, ERK, which can be decreased by treatment with CK2 inhibitor quinalizarin.

Conclusion

Progestogen-induced proliferation of MCF-7 cells is associated with rapid phosphorylation of PGRMC1. CK2-binding site is essential for activation of PGRMC1. PGRMC1 Ser181 point mutation may induce phosphorylation of AKT, ERK, suggesting that PGRMC1 promotes breast cancer proliferation through activation of AKT pathway. Overall, this study provides a new insight in PGRMC1-mediated AKT signaling promoting the proliferation of breast cancer cells.

Keywords PGRMC1, phosphorylation, AKT

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Funding:National Natural Science Foundation of China (81671411); first batch of Beijing maternal and child health specialist demonstration units "menopausal health specialist" (2018/01-2020/12)

Topic: 8.6 New prognostic and predictive factors

P334 Role of the tumor microenvironment in the development of DCIS to invasive breast cancer and identification of possible biomarkers to predict that progression in 3D co-culture models

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Context
Ductal carcinoma in situ (DCIS) progresses in 13-50% of the cases in an invasive ductal carcinoma (IDC). The individual progression risk from DCIS to IDC can not be estimated based on clinical parameters or biomarkers and as a result all patients with DCIS are treated equally. Identification of DCIS lesions with a high or low risk of progression would enable personalized oncological treatment avoiding overtherapy.

Objective
The role of the tumor microenvironment appears to be critical in the development of an invasive phenotype. Therefore, the role of tumor associated fibroblasts (TAFs) and of cells of the immune system has been further investigated. Further goal is to identify biomarkers that could predict that progression.

Methods
Co-cultures of primary fibroblasts with MCF10DCIS.com cells and of Lymphoblasts (U937) with MCF10DCIS.com cells were grown in a 3D co-culture system. Primary fibroblasts were isolated from benign or malignant breast biopsies and were cultured in a type I collagen layer beneath a Matrigel layer with MCF10DCIS.com cells. In both layers, dye-quenched fluorescent collagen was used to demonstrate proteolysis. The lymphoblasts were cultured in the medium over a Matrigel layer with MCF10DCIS.com cells. The 3D co-cultures were examined under the laser scanning confocal microscope to reveal possible morphological changes indicating the transition from an in situ to an invasive phenotype. PCR for a variety of proliferation, invasion and apoptotic markers to reveal possible predictive markers is planned.

Main outcome
MCF10DCIS.com cells in co-culture with healthy fibroblasts form smooth and round spheroids.The spheroids in co-culture with TAFs are morphologically different: the cells are no longer compact in the spheroid, but break star-shaped out of the structure, resembling invasive cells.

Results
Moreover, TAFs have a higher proteolytic potential compared to healthy fibroblasts and the distance between fibroblast and MCF10DCIS.com cells decreases over time. The co-culture with lymphoblasts significantly influences the circularity of the spheroids.

Conclusions
Our data suggest an important role of TAFs and cells of the immune system in the development of DCIS to IDC. Results of PCR of different markers to reveal the reflection of these observations on molecular level are pending. Our model can be used to further invastigate the pathways leading to invasive disease and identify biomarkers to predict the progression.

Topic: 8.7 Anti-estrogens, SERMs and aromatase inhibitors

P335 Incidence of breast cancer in VVA patients treated with ospemifene and the similar patients without any VVA related treatments in the US

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Ospemifene has been marketed in the US since 2013 to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy (VVA) due to menopause. This study used real-world data to estimate the incidence rates of breast cancer in VVA patients without a history of breast cancer treated with ospemifene, and in compatible VVA patients without any VVA related treatment.

VVA patients were identified from 2011-2018 US MarketScan Commercial and Medicare Supplemental insurance claims database. Those received ≥1 ospemifene after the first VVA diagnoses were considered as treated. Those without any VVA related treatment after the first VVA diagnosis were considered as controls. The date of first VVA diagnosis was the index VVA date. Each treated patient was matched to ≥1 control(s) on age, index VVA year, geographic region, and the follow-up period from the index VVA to last available data. The date of first dispensing ospemifene (index treatment date) in a treated was copied to her matched controls as pseudo index treatment date. All subjects must have ≥ 1-year baseline data before the index VVA date and ≥ 1-year follow-up data after the index treatment date, and no evidence of breast cancer before index treatment date. Breast cancer after the index treatment date was identified by breast cancer diagnosis codes, mastectomy, chemotherapy, or radiation procedure. Incidence rate, rate ratio (RR) and their 95% confidence intervals (CI) were calculated. The analyses were repeated in a subset of subjects after matching 1 treated with 2 untreated additionally on baseline Charlson Comorbidity categories.

2,622 ospemifene users and 26,917 untreated VVA patients met the inclusion/exclusion and matching criteria. Average days ospemifene supplied was 306 days (Standard deviation [SD]=331). Average follow-up time from index treatment was 937 days (SD=392) for treated and 915 days (SD=396) for controls. 19 treated and 236 controls met breast cancer definition after the index treatment date. The breast cancer incidence rate per 1,000 person-year (PY) was 2.83 (95%CI: 1.81-4.44) for treated subjects and 3.51 (95%CI: 3.09-3.99) for controls (RR= 0.81, 95%CI: 0.51-1.29).

After 1:2 matching, the incidence rate per 1,000 PY was 2.03 (95%CI: 1.06-3.91) for treated and 3.53 (95%CI: 2.49-4.99) for controls (RR=0.58, 95%CI: 0.28-1.21).

The study did not show an increased risk of breast cancer in ospemifene users comparing to compatible untreated VVA patients in various analyses.

Topic: 8.8 Oncological and aesthetic breast surgery

P336 Breast prosthesis rupture silicone migration lymphadenopathy: case report

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Context

Silicone implants have been widely used for breast augmentation and reconstruction for over 40 years. Although its initial reputation as a biologically inert material, it has been related with numerous complications, such as rupture and granulomatous inflammatory reactions. Silicone lymphadenopathy after implantation is an uncommon complication, due to the release or migration of silicone into the tissues surrounding the breast implant. In the last 31 years only 10 articles correlate breast implant rupture with consequent silicone migration to lymph nodes. In general, the diagnosis is made accidentally during examination after breast carcinoma mastectomy or patients seek service because of pain or some unevenness in the breast.

Objective

To report a rare case of foreign body granulomatous lymphadenitis associated with silicone breast implant rupture.

Patient

We report a case involving a 38-year-old woman, without comorbities, that underwent a mastopexy 13 years ago and replaced the breast prosthesis in 2013. 6 years later, preventive exams showed rupture of the right prosthesis and some months later a lump was detected in the right axilla during a routine consultation. A bilateral mammogram for silicone implant screening showed regular contoured implants with no signs of ruptures, no nodules, sparse calcifications, and axillary extensions without peculiarities. A magnetic resonance imaging demonstrated right silicone breast implant with signs suggesting intra and extracapsular rupture, as well as silicone migration into the axillary lymph nodes. An aspiration puncture was performed and no signs of malignancy were observed, but characteristics compatible with granulomatous lymphadenitis of foreign body type.

Conclusion

Breast prosthesis rupture is a rare complication of cosmetic or reconstructive procedures involving silicone. Silicone lymphadenopathy after implantation is an even more uncommon complication due to the release or migration of silicone into the tissues surrounding the implant. This case study corroborates that silicone lymphadenopathy after breast augmentation mainly affects axillary lymph nodes. We highlight the need to employ a clinical suspicion in order to exclude malignancies. Furthermore, this case reinforces the importance of good imaging as an useful initial investigation that should be followed by fine-needle aspiration cytology and, when necessary, excisional biopsy and histological analysis for more information.

Topic: 9.4 Laparoscopic treatment of pelvic masses

P339 Innovative evidence of laparoscopic-assisted myomectomy with in-bag extraction effectiveness cell blocks and immunohistochemical investigation

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Context

Despite the benefits of laparoscopic technique due to minimally-invasive myomectomy, morcellation of tumor tissues in the peritoneal cavity may leave tiny fibroid fragments which spilling into the peritoneal cavity. They can give birth to parasitic peritoneal myomas, so-called "morcellomas' or dissemination of unexpected occult malignancy during tissue extraction with morcellation can occur. Consequently, we can suppose that using retriever bags can protect surgical spilling and prevent these conditions.

Objective

We investigated peritoneal washings cytologically before and after myomectomy to prove laparoscopic-assisted myomectomy with in-bag manual tissue extraction effectiveness and safety.

Patients

30 women have classical laparoscopic miomectomy (n=10), laparoscopic-assisted myomectomy with in-bag manual tissue extraction (n=10) and laparotomic myomectomy (n=10) done.

Interventions

We performed laparoscopic and laparotomic myomectomy, peritoneal washing, cell blocks preparation and evaluation histologically and immunohistochemically (with smooth muscle actin antibody).

Main outcome measures and Results

Peritoneal washing performed thrice: after entering into peritoneal cavity, after myomectomy, after morcellation (in laparoscopic interventions). In cell blocks of peritoneal washing material fusiform cells were detected in all groups of patients. In patients who have classical laporoscopy done, they were revealed in 6 cases (in 1 patient after myomectomy and in 5 after morcellation). In patients who have laparoscopic-assisted myomectomy with in-bag manual tissue extraction done, we revealed these cells in 4 cases (in 1 patients after miomectomy and in 3 after morcellation). In patients who have laparotomy done, we revealed fusion cells in 7 patients (in 2 patients after surgical cut, in 5 – after myomectomy). In all cases with proved fusion cells in cell blocks we confirmed their smooth muscle nature immunohistochemically.

Conclusions

The minimal quantity of smooth muscle cells were revealed after laparoscopic-assisted myomectomy with in-bag manual tissue extraction proving the effectiveness of this method to reduce the potential risk of tumor cell dissemination.

Topic: 9.5 Laparoscopy, endometriosis and reproduction

P341 Non-communicating uterine horn presenting with endometriosis soon after menarche

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Context
Intense and precocious dysmenorrhea is usually related to obstructed menstrual flow.

Objetive
To report a case with very intense dysmenorrhea since menarche related to menstrual flow obstruction and endometriosis

Methods
Case report

Patient
A 12-year-old girl consulted because of very intense dysmenorrhea since menarche 6 months earlier. She had 3 periods before the appointment and reported the necessity to present to emergency care because of intense pain leading to collapse. Ultrasound identified an uterus didelphys. The right horn measured 7.4 x 3.4 x 3.1 cm and the left one 6.8 x 3.2 x 3.0 cm. The right ovary measured 4.2 x 1.9 x 2.1 (8.3 ml) and the left ovary measured 2.8 x 1.9 x 1.8cm (4.8ml). The endometrium in both cavities measured 0.8cm. Continuous oral combined contraceptive was prescribed. She had spotting 3 months later and again had a very intense dysmenorrhea with collapse. A MRI was performed and no additional findings were observed.

Intervention
The patient was then submitted to a laparoscopy, which confirmed a didelphys uterus. The right horn was slightly larger than the left one and some foci of endometriosis in the right ovary were observed. In view of these findings, a decision was made to perform a complementary hysteroscopy to rule out a mullerian obstruction. At hysterocopy, a single normal cervix was identified, with a normal left uterine horn but also a non-communicating right uterine horn. The patient was subsequently submitted to a hemihysterectomy on the right side. We could then confirm the non-communicating right uterine horn related to a ipsilateral cervical agenesis.

Results
At the moment the patient is 4 months post-surgery and free of dysmenorrhea.

Conclusion
Any patient who reports a very intense dysmenorrhea since menarche should have menstrual flow obstruction ruled out as a cause, even when a hematometra is not observed at initial presentation.

Topic: 9.6 New treatments of uterine myomas

P343 Treatment of patient with uterine fibroid with Focused Ultrasound Surgery – clinical case

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Objective

Focused ultrasound surgery (FUS) is taking part of the clinical gynecological practice over the last 10 years. Treatment of uterine fibroids using high-intensity focused ultrasound (HIFU) is an organ-sparing, non-invasive and thermoablative procedure that is applied transcutaneously. In this ablation, the fibroid is gradually heated under ultradound monitoring in small, focussed stages, until temperature reaches 60°C and more and complete denaturation of the localised tumour occurs. Our aim is to present a clinical case about a patient with uterine fibroid who underwent FUS with HIFU therapy with very good therapeutic responce, assessed with MRI and certified questionnaire about the Quality of life assessment.

Methods

43 years old patient with clinical, ultrasound and MRI data for uterine fibroid, proving fibroid on the posterior uterine wall with size 73x71x74mm (125ml) was treated with FUS. After standart preparation, the patient was placed at the HIFU table. The uterine fibroid was found and then treated with High Intensity Focused Ultrasound (HIIFU) beams. The maximum energy was 400W. Average energy output was 381W, total sonication time of the procedure was 526 seconds. The total energy was 200500J. The next day the patient was discharged in good general condition, without subjective complaints, afebrile, with antibiotic prophylaxis for 5 days.

Results

At the control MRI of the pelvis after 45 days we found that the fibroid reduced its volume by 25% and had over 90% necrosis. The Quality of life of the patient was assessed by using Uterine Fibroid Symptom and Health Related Quality-of-Life Questionnaire.

Conclusion

The presented clinical case is a good example for the therapeutic possibilities of FUS in patients with uterine fibroids. Future prospective investigations in this area are needed.

Topic: 10.1 Ultrasound in gynecology and obstetrics

P344 Rectal water contrast transvaginal ultrasonography versus computed colonography for the diagnosis of rectosigmoid endometriosis: a prospective comparative study

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Context

Rectosigmoid involvement by endometriosis causes intestinal symptoms such as constipation, diarrhea, and dyschezia. A non-invasive diagnosis of bowel endometriosis is relevant to provide the patients information on the potential hormonal or surgical treatments.

Objectives

The objective of the current study was to compare the performance of three-dimensional rectal water contrast transvaginal ultrasonography (3D-RWC-TVS) and computed colonography (CTC) in predicting the presence and characteristics of rectosigmoid endometriosis.

Methods

This prospective study included patients with suspicion of rectosigmoid endometriosis who underwent both 3D-RWC-TVS and CTC and subsequently were surgically. The findings of imaging techniques were compared with surgical and histological results.

Results

Out of 68 women included in the study, 37 (48.9; 95% C.I. 38.2%-59.7%) had rectosigmoid nodules and underwent bowel surgery. There was no significant difference in the accuracy of 3D-RWC-TVS and CTC in diagnosing the presence of rectosigmoid endometriotic nodules ($p = 0.118$), although CTC was more precise in diagnosing endometriosis located in sigmoid ($p = 0.016$). 3D-RWC-TVS and CTC estimated similarly the largest diameter of the main endometriotic nodule ($p = 0.077$). CTC was more accurate in estimating the distance between distance between the lower margin of the intestinal nodule and the anal verge ($p < 0.030$) but was less tolerated than 3D-RWC-TVS ($p < 0.001$).

Conclusion

3D-RWC-TVS and CTC have similar diagnostic performance for the diagnosis of rectosigmoid involvement of endometriosis, although the ultrasonographic exam is less accurate in diagnosing sigmoid nodules. CTC may be combined with 3D-RWC-TVS because of the high diagnostic performance in detecting rectosigmoid endometriosis and the ability to diagnose endometriotic nodules located above the sigmoid.

Topic: 10.1 Ultrasound in gynecology and obstetrics

P345 The utility of HD-flow analysis in the differential diagnosis of ovarian tumors

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Objective

Modern ultrasound scanners are equipped with high quality techniques for the assessment of tumor blood flow, however, their utility in differential diagnosis of ovarian tumors (DDOT) is not known. The main aim of our study was to evaluated the utility of HD-flow analysis in DDOT.

Methods

The study group included 94 malignant and 50 benign patients diagnosed in Private Medical Practice Dariusz Szpurek due to ovarian tumor. The patients underwent ultrasound examination according to the International Ovarian Tumor Analysis (IOTA) group guidelines. The ultrasonography was performed using Voluson E6, with HD-Flow technique used for vascularization assessment. All of the patients underwent adequate surgical treatment. We have developed decision tree model to differentiate malignant from benign ovarian tumors. The model was prospectively validated on the group of 35 benign and 25 malignant ovarian tumor patients.

Results

The following features significantly discriminated between benign and malignant ovarian tumors: tumor vascularization (attribute importance: 97%), presence of solid elements (79%), patient age (58%), tumor structure (46%), menopausal status (4%). The model achieved: The area under ROC curve (AUC) of 0.811, diagnostic odds ratio (DOR) 21.185, sensitivity (SENS) 88%, specificity (SPEC) 74.3%, positive predictive value (PPV) 0.71, and negative predictive value (NPV) 89.7%. In the prospective validation the model reached: AUC = 0.806, DOR 20.113, SENS 87%, SPEC 76%, PPV 69% and NPV 90%.

Conclusions

Tumor vascularization assessed by HD-flow technique differentiate benign from malignant tumors. The proposed diagnostic tree model incorporating HD-flow analysis may be useful for DDOT.

Topic: 10.1 Ultrasound in gynecology and obstetrics

P346 Accuracy of transvaginal ultrasound for detection of deep infiltrating endometriosis

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Context
Endometriosis is characterized as the occurrence of endometrial tissue, outside the uterine cavity. Although the gold standard for diagnosis of endometriosis is histological, imaging studies such as transrectal ultrasound, transvaginal ultrasound and magnetic nuclear resonance are acquiring an important role in the diagnosis of endometriosis, allowing the mapping of pelvic lesions and follow-up of women in case of clinical treatment of the disease

Objective
To evaluate the accuracy of transvaginal ultrasound in the diagnosis of deep infiltrating endometriosis (DIE).

Methods
Retrospective study. Patients:65 women with DIE.

Interventios
All women underwent transvaginal ultrasound with bowel preparation prior to surgery.

Main outcome measure
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of transvaginal ultrasound for the diagnosis of DIE. The surgery was used as the gold standard.

Results
The mean age of women was 39.71 ± 6.31 years. Ultrasound had a sensitivity of 73%, specificity of 84%, PPV of 80%, NPV of 78% and an accuracy of 79% for the diagnosis of adnexal lesions and had a sensitivity of 77% and 37%, specificity of 65% and 96%, PPV of 82% and 60% NPV of 57% and 92% and accuracy of 79% and 90% for the diagnosis of bowel and bladder lesions respectively.

Conclusion
Transvaginal ultrasound is a effective method for the diagnosis of deep infiltrating endometriosis lesions.

Topic: 10.2 Interventional ultrasound techniques

P347 Outcome in women undergoing uterine artery embolization fo arterio-venous malformation following pregnancy

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Objective

To analyse the outcome in cases of symptomatic arterio-venous malformation (AVM), after abortion or delivery, conservatively managed by uterine artery embolization (UAE).

Method

From January 2018 to June, 2019, 18 cases of post pregnancy uterine AVM were diagnosed and underwent UAE for management. Follow up data is available for 15 cases, it ranged from 6 to 24 months. Medical records were reviewed for the indication of UAE, presenting symptoms, post UAE complications and subsequent fertility. Trans-Vaginal Sonography with doppler confirmed the diagnosis, 7 women also underwent a MRI examination.

Results

The mean age was 27 years and mean parity was 1.3. Out of 18 cases, 14 (77.7%) presented after abortion, 2 of these were after second trimester abortion. Medical abortion was seen in 7, surgical evacuation in 4 and spontaneous abortion in 3 patients. 12 women underwent D&C for retained products. 4 patients (22.3%) had full term normal vaginal delivery and presented with secondary PPH, out of them 2 patient had undergone D&C for RPOC. 13 patients presented with continuous BPV post abortion or delivery and five patients had irregular bleeding. Duration of symptoms ranged from 22 days to 8 months. Bleeding was controlled in all patients after UAE except for 1 patient who required repeat UAE one month later. Post embolization syndrome occurred in two patients, managed with antipyretics and pain killers. 15 patients could be followed up, bleeding stopped in an average 5.1 days and all resumed normal menstruation. On subsequent follow up 6 patients developed abnormal vaginal bleeding. 8 patients tried for conception, out of them 5 (62.5%) got pregnant. Two women carried pregnancy till term and two had preterm delivery and one had spontaneous abortion. Three women delivered by cesarean and one delivered vaginally. Two patients had postpartum hemorrhage which was managed medically.

Conclusion

UAE for management of symptomatic AVMs post pregnancy is an attractive treatment modality. It gave symptomatic relief in majority of women and did not impair fertility.

Topic: 10.3 Hysteroscopy

P348 Other uses of entonox in gynaecology

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We know Entonox is useful in labour pain management. We know about its minimal second effects. But what we don't know yet is how else we could use it to our advantage. We analysed a series of randomized trials about the use of Entonox. Their results are promising. A series of procedures such as transrectal ultrasonography guided prostatic biopsy, cystoscopy and extracorporeal shock wave lithotripsy are done under the analgesic effect of entonox. Other reports show good compliance of paediatric patients using entonox in pain producing procedures. The same applies for colonoscopy or percutaneous biopsies.
We analysed what kind of procedures and their number during the last year will benefit from entonox use in our clinic. We already use entonox for labour pain in our hospital. In our clinic we perform around 700 d&c for miscarriages, 900 ovarian puncture for art, 871 hysteroscopy with general anaesthesia, 600 hysteroscopy without anaesthetic, 400 d&c for endometrial biopsies. We estimated that all of d&c and ovarian puncture could benefit from the use of entonox instead of no analgesia or general analgesia usage. This will increase the patient comfort and reduce the costs of the procedures. As for the hysteroscopies, at least 50% of them could benefit from the use of entonox.
In conclusion we strongly advice using Entonox for other procedures than pain labour management.

Topic: 10.3 Hysteroscopy

P349 An experience of endoscopic treatment of the postoperative scar‘s “recess” after cesarean section

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Relevance

Cesarean section (CS) frequency increased by 20% in recent years, increasing actuality of the problem of a “recess” in the post-operation scar area that often might be a cause of symptoms like abnormal uterine bleeding (AUB), dysmenorrhea, chronic pelvic pain, dyspareunia, infertility and risk of many obstetric complications.

Goal of research

Evaluation of hysteroscopic treatment’s effectiveness of a “recess” after CS.

Materials and methods

An examination of 34 patients was conducted. These patients have undergone a hysteroscopic dissection of edges with the coagulation of “recess” bottom. This pathology was diagnosed through the ultrasound examination with the usage of a vaginal transducer.

Anormal uterine bleedings (AUB) of 21(61%) women and endometrial polyps of 13 (38%) women were the indications for hysteroscopy. After the provided hysteroscopic treatment, the frequency of chronic pelvic pain decreased by 75%, AUB – by 86%, of dyspareunia – by 40%. Three months after hysteroscopy the average thickness of myometrium in the area of post-CS’ scar increased from 3,9±1,0 mm to 6,3±0,9 mm ($p<0,05$) according to ultrasound data. Laparoscopic dissection of “niche” with a myometrium recovery was provided in two cases where the thickness of residual myometrium was less than 3,0 mm, and patients had reproductive plans. 3 out of 7 patients with infertility had an independent pregnancy. Two of them were delivered in 39 weeks by CS in a planned manner. And one woman is at an early stage in pregnancy now.

Conclusions

An endoscopic treatment of the “recess” after CS helps to reduce clinical symptoms, improving the quality of a woman’s life and her fertile function. Moreover, it decreases risks of obstetric complications during next pregnancy.

Key words: the postoperative scar‘s “recess” after cesarean section, AUB, dyspareunia, chronic pelvic pain, hysteroscopy.

Topic: 10.3 Hysteroscopy

P350 Diagnostic management of high-thromboembolic-risk patients with abnormal uterine bleeding

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Context

Abnormal uterine bleeding affects more than 20% of women taking oral anticoagulants. Patients with deep venous thrombosis require long-term anticoagulant therapy to prevent recurrent thromembolism; the most common used oral anticoagulant is vitamin K agonist. Hysteroscopy is the gold standard of evaluation of the cervical canal and the uterine cavity, it provides the most accurate diagnostic for endocervical and endometrial pathology and intracavitary masses.

Aim

To assess the use of hysteroscopy in the management of uterine bleeding.

Method

We perform a prospective observational case series of 14 women receiving oral anticoagulant therapy with vitamin K antagonists (acenocumarol) for over 18 month after major deep venous thombosis that presented with abnormal uterine bleeding (intermenstrual bleeding and menorrhagia). All the 8 women were parous, age between 36 and 43 years, with ereditary thombophilia, with no gynecologic history and were regulary followed-up by the cardiologist. After physical examination and transvaginal pelvic ultrasound, hysteroscopic exploration was decided. In order to perform it, bridging therapy with low-molecular-weight heparin was decided. Oral anticoagulants were stopped 5 days before the procedure and continued 1 day after. In all 14 patiens endometrial and endocervical biopsy was performed.

Results

Diagnostic hysteroscopy revealed intrauterine pathology in 10 of 14 patients: submucosal fibroids in 1 patients, endometrial hyperplasia in 4 patients, endometrial polyps in 3 patients, multiple small intramural fibroids in 1 patients, endometrial atrophy in 1 patients. The hysteroscopic findings correlated with the histopathologic findings (endometrial fragments obtained by endometrial biopsy and fibroids and polyps trated by hysteroscopic resection): endometrial hyperplasia 4 cases, endometrial atrophy 1 case, endometrial polyp 3 cases, submucous myoma 1 case, normal endometrium - proliferative or secretory in 4 cases. In 3 cases of endometrial hyperplasia we performed hysteroscopic endometrial ablation, in 7 cases progestin therapy was initiated and in 4 patients a levonorgestrel intrauterin device was inserted.

Conclusions

The management of uterine bleeding in high-thromboembolic-risk patients on oral anticoagulants is challenging. Hysteroscopy represents for these women an accurate diagnostic tool and also provides important therapeutic options.

Topic: 10.4 Colposcopy

P352 The analysis of pathology of cervix of women in the period of perimenopause

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Aim

The aim of the research is to study the structure of the neck of uterus of women who are at the age of perimenopause.

Material

120 patients, aged 45-52, with different abnormalities of the neck of uterus underwent complete clinical-laboratory examination. In consideration of revealed bacterial-virus infection patients' vaginas were sanitized and antibacterial, antiviral therapeutic measures were carried out. Control determination of antibody titers to chlamydia and ureaplasma performed in 1.5-2 month period of time after complete course of treatment.

Results

Most of the patients – 110 (91,7%) had hypertrophy of the neck of uterus which is the manifestation of cervicitis. Every forth observed patient had a diagnose of deformation of the neck of uterus with old hysterorrhexis – 29 (24,2%), 21 (17,5%) women had cicatricial deformity of the neck of uterus. Hypertrophy of the neck of uterus dominates in the structure of its pathology which is the evident of inflammation processes taken place in the neck of uterus in the past. On colposcopy 34,2% of patients were diagnosed ectopia of columnar epithelium with atypical transformative area. Benign area of transformation was observed in 28,3%. Cytological atrophic cervicitis and vaginitis were verified and confirmed in 17,5% of patients.

After cutting off laboratory and clinical manifestations of vaginitis and receiving negative take to bacterial and virus infection, Papanikolau cytological study of the smear was carried out on the second stage. The following findings were taken: negative for intraepithelial damage and malignant was found in 52 patients (43,3%). Among them 36 have reactive changes of epithelial cell caused by inflammation, and also cytological symptoms subatrophy of the mucous membrane of the neck of uterus. The other 68 (56,7%) patients had pathology of epithelial cell; atypical squamous cell of ambiguous importance (ASCUS) in 12 (17,6) patients; low level of squamous cell impairment in 26 (38,2%) among them CIN II in 19 (27,9%), CIN III in 11 (16,2%). Patients with CIN II and CIN III were directed on biopsy of the neck of uterus for thorough diagnosis of pathological condition.

Conclusion

Received findings of the study show the importance of thorough medical examination of the patients at the age of perimenopause in order to prevent oncological troubles

Topic: 10.5 Laparoscopy

P353 A comparative analysis between unidirectional barbed versus conventional vicryl suture for vaginal cuff closure in cases of total laparoscopic hysterectomy

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Study Objective
We compared the use of unidirectional barbed sutures and conventional vicryl sutures for vaginal cuff closure during total laparoscopic hysterectomy. The aim of our study is to evaluate whether the use of unidirectional barbed suture (V-Loc) for vaginal cuff closure is associated with a decrease in vault closure time, operative time, blood loss, and other intraoperative and postoperative complications compared to polyglactin 910 (Vicryl) in patients undergoing total laparoscopic hysterectomy for benign pathology.

Methods
We performed a prospective comparative study among patients who underwent total laparoscopic hysterectomy between July 2018 and March 2019 at our unit at AIIMS, Rishikesh.

Results
A total of 110 women were studied: 65 were in the vicryl group, and 45 were in the barbed suture group. The mean vault closure time was significantly less with barbed suture (8.84 min) than vicryl group (11.68 min). The mean number of stitches taken was more in barbed suture group (7.46) than vicryl group (6.95), though the difference was not statistically significant. No statistically significant differences were found in operative time, or postoperative outcomes, such as vaginal cuff dehiscence, infectious complications, and the presence of granulation tissue.

Conclusion
The efficacy and safety of unidirectional barbed suture is comparable to the conventional vicryl sutures. Barbed sutures can be safely used to reduce procedure time and surgical difficulty.

Topic: 10.5 Laparoscopy

P354 Pregnancy-related deciduosis: diagnostics and clinical implications

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Background

Formation of ectopic decidua (deciduosis) during gestation is a welldocumented phenomenon that has been caused by decidualization of a preexisting ectopic endometrium or rapid enlargement of endometrial tissue differentiated from pluripotential cells in response to pregnancy. Largely deciduosis is a benign process without any clinical consequences. However decidualized tissue can grow rapid during pregnancy to acquire a gross appearance that macroscopically mimics a malignancy.
The aim of this study was to evaluate the histopathological and immunohistochemical characteristics of ectopic decidua found in the peritoneum during a surgical intervention and to emphasize the value of their correct laparoscopic assessment.

Material and methods

We retrospectively analyzed pathology reports that included a diagnosis of deciduosis on surgical resection specimens over a 5-year period between 2014 and 2018 2014 in Department of Pathology, Center of family planning and reproduction. The clinical features of the cases were obtained from their clinical folders. To confirm the morphological conclusion of deciduosis we were retrieve from the pathology archives available paraffin-embedded tissues for immunohistochemical evaluations with CD10 and Vimentin.

Results

Decidualized endometriomas were found in 45 women, variable size foci of ovarian deciduosis consisted of round cells with small nuclei and abundant eosinophilic cytoplasm without nuclear atypia were reviled in 23 patients, ectopic decidua of fallopian tubes – in 7, deciduosis of appendix – in 1, decidual transformation of omentum – in 7. One patient presented with diffuse peritoneal deciduosis twice a 3 year that were incidentally found during a cesarean section. All the times the intraoperative appearance suggested peritoneal carcinomatosis. Immunohistochemical staining showed positive staining of the cell cytoplasm with vimentin and CD10.

Conclusion

Deciduosis detection is usually an incidental finding on histology of peritoneal biopsies taken during Caesarean sections. Immunohistochemistry may help the differential diagnosis of peritoneal deciduosis where problems are experienced differentiating the case from malignant tumors. It could be taken into account during laparoscopy because of cancer mimics.

Sponsored Key Lectures

Clinical benefits of Hydeal-D® in the non-hormonal treatment of vaginal atrophy (Sponsored by Fidia Farmaceutici)

Clinical benefits of Hydeal-D® in the non-hormonal treatment of vaginal atrophy

Rossella E. Nappi (IT)

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Vulvovaginal atrophy (VVA) is a chronic and progressive condition, which is an integral part of the Genitourinary Menopause Syndrome, occurring in approximately 50% of postmenopausal women. The most common symptoms include vaginal dryness and dyspareunia followed by irritation, burning, itching, discharge, urinary discomfort and bleeding with intercourse. Several therapeutic strategies may be used for the management of VVA: lifestyle modification, non-pharmacological therapies, hormonal and non-hormonal treatments (lubricants and vaginal moisturizers). The latter, used alone or in combination with other therapies, are especially indicated in patients who wish to avoid the use of hormonal therapy, for concern related to the onset of potential side effects or in women who have a contraindication to the estrogens' use. Among vaginal moisturizers, gel and vaginal pessaries containing Hydeal-D® (Fidia Farmaceutici), a hyaluronic acid (HA) ester, are available for the treatment of vaginal dryness of various origin and as adjuvant in the natural healing process of friction-induced microlesions in the vaginal mucosa. Hydeal-D® is a HA modified to resist longer the degradation caused by hyaluronidase enzymes acting in the vaginal mucosa. The progressive hydrolysis of the ester bond ensures slow and continuous release of native HA in the MW 200 KDa fraction, which has mucoadhesive properties and has shown to be active in the tissue repair processes. In a recent prospective, multicenter clinical trial, a 3 months treatment with Hydeal-D® vaginal pessaries applied every 3 days, has been found effective and safe in the improvement of VVA sign and symptoms in 40 postmenopausal women, both after 1 and 3 months of treatment. Changes from baseline confirmed a significant improvement in all parameters analyzed, including VHI, vaginal pH, VMI, patient's perception of VVA symptoms and sexual function (FSFI, FSDS-R). Moreover, after 3 months of treatment, the improvement exceeded the threshold values of the VVA diagnosis, as well as of sexual dysfunction and distress, confirming a clinically relevant improvement in the VVA symptoms. The gel formulation based on Hydeal-D® has been recently tested in a pilot study in postmenopausal breast cancer survivors with VVA, to evaluate the reduction of vaginal dryness and the prevention of sexual dysfunction. Results support the hypothesis that early intervention may decrease the decline in sexual function caused by aromatase inhibitors' therapy. The significant improvement of VVA-related signs and symptoms indicates that Hydeal-D®-based formulations are effective non-hormonal therapeutic options, safe and well tolerated for VVA of different nature, especially in postmenopausal women.

(Sponsored by Serelys Pharma)

Purified and specific cytoplasmic pollen extract, a non-hormonal alternative for the treatment of menopausal symptoms

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Context

Research into non-hormonal alternative therapies is necessary for women for whom Menopausal Hormone Therapy is contraindicated or for women who don't want to take hormones.

Objective

This presentation focuses on one of those non-hormonal options called Purified and Specific Cytoplasmic Pollen Extract, PureCyTonin®.

Methods

It has been evaluated in several preclinical and clinical studies where it demonstrated its value as a safe and non-estrogenic alternative for menopause.

Results

Beneficial effects of PureCyTonin® in the treatment of menopausal symptoms like hot flushes in healthy women as well as in premenstrual syndrome are described. Its mechanism of action, as a SSRI 'like' therapy is also discussed in this presenatation. The lack of estrogenic effect demonstrated in preclinical studies suggests that purified and specific pollen extract can be also a suitable option managing menopausal symptoms in women with breast cancer.

Sponsored Meet the Experts

Evidence-based phytotherapy: effective and safe treatments for women health (sponsored by Bionorica)

Evidence-based phytotherapy in the treatment of cycle disorders and menopausal symptoms

Andrea R. Genazzani (IT)
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Diseases such as menstrual cycle disorders, premenstrual syndrome (PMS), mastodynia and menopausal symptoms are the result of endocrine disorders that impair women's well-being. Fortunately, herbal medicines have been shown to effectively and safely relieve these disorders and can be regarded as evidence-based medicines that can even replace hormonal preparations, which are often used to treat these symptoms.

This presentation, refers two well-studied plant extracts, Vitex agnus castus (VAC) and Black Cohosh/Cimicifuga racemose (CR), which have been shown to restore hormonal balance and improve women's quality of life from menarche to menopause.

Vitex agnus-castus is particularly known for its ability to improve conditions affecting a woman's reproductive system. One of the most popular and well-researched attributes of VAC is its ability to reduce symptoms of PMS, such as mastodynia and emotional imbalance. VAC works by lowering the elevated level of the hormone prolactin. This helps rebalance other hormones, including estrogen and progesterone — thus restoring hormonal balance. Diterpenes isolated from the special VAC extract BNO 1095 (Agnucaston®, Cyclodynon®) have been shown to mimic dopamine, known to regulate prolactin.

The majority of women aged 45-60 years suffer from menopausal symptoms, especially hot flushes and night sweats. It is known that a low level of neurotransmitters causes these symptoms. Serotonin, GABA- and dopamine agonists have been isolated from a special extract of the rhizome of CR, which may explain its mechanism of action. In several clinical studies, the CR extract shows good efficacy, leading to a significant reduction in hot flushes and other menopausal complaints. Studies have also shown excellent safety (e.g. no effect on the endometrium or liver enzymes) for the special extract CR BNO 1055 (Klimadynon®), which was better than conjugated estrogens.

Conclusion

The use of standardised phytopreparations based on VAC, such as the special extract BNO 1095 can be regarded as an important component of the complex therapy of female reproductive diseases in women, especially in cases of increased stress leading to increased prolactin levels.

For menopausal symptoms approved Cimicifuga preparations, such as the special extract BNO 1055 are a safe and effective treatment option.

Evidence-based phytotherapy: effective and safe treatments for women health (sponsored by Bionorica)

Do we need always antibiotic therapy to treat uncomplicated cystitis in female patients?

Kurt Naber (DE)
Technical University Munich School of Medicin, Germany

Urinary tract infections (UTIs) are among the most common bacterial infections. They represent a considerable social burden, especially for women. About 40% of all women experience at least one UTI during their lifetime. About one-third of women who have already had a UTI suffer from recurrent UTI (rUTI).

A clinically symptomatic UTI must be distinguished from asymptomatic bacteriuria (ABU). As a rule, no therapy of ABU is required. There are only two exceptions: treatment of ABU in pregnancy and before traumatizing urological interventions.

In order to combat the overuse of antibiotics (Abs) and thus the rising rates of antimicrobial resistance, it is important to establish efficacious substitutes for Abs in the treatment of acute, lower uncomplicated UTIs (uUTIs). Previous studies have compared the efficacy of alternatives such as the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen and diclofenac with ABs, and have shown promising efficacy results. However, non-inferiority remains to be established.

Another approach is the phytotherapy, e.g. with BNO 1045 (Canephron®N, Bionorica SE, Neumarkt), containing centaury powder (Centaurii herba), lovage root powder (Levistici radix) and rosemary leaf powder (Rosmarini folium). In preclinical studies its anti-inflammatory and spasmolytic properties could be established. In a pilot study including 125 women with typical symptoms of acute uncomplicated cystitis a cure rate of 71.2% was achieved after one week of treatment without recurrence up to 37 days of follow up.

In a recently published, randomised, double-blind, phase III non-inferiority clinical trial, BNO 1045 was compared for 7 days with a single dose of fosfomycin trometamol (FT) in the treatment of acute uUTIs. The primary endpoint was the proportion of patients who received ABs to treat uUTIs between days 1 and 38. Between days 1and 38, 238 (83.5%) patients in the BNO 1045 group and 272 (89.8%) patients in the FT group received no ABs. At a 15% non-inferiority margin, BNO 1045 was non-inferior to FT in treating acute, lower uUTIs. The secondary endpoint of the study was the decrease in symptoms, which was nearly overlapping in both study arms using the ACSS questionaire.

Conclusion

Overall, it could be demonstrated that symptomatic treatment with an evidence-based phytotherapeutic agent can be a viable alternative to ABs for the treatment of acute lower uUTIs and can potentially help to reduce the use of ABs and antibiotic resistance.

Sponsored Symposia

E4 - It is time for a Renaissance in Oral Contraception (REn4issance) (sponsored by Gedeon Richter and Mithra Pharmaceuticals)

Why does oral contraception need a renaissance?

Jean-Michel Foidart (BE)
University of Liège and Mithra Pharmaceuticals

Estetrol (E4) is a native and naturally occurring estrogen exclusively produced during human pregnancy, unlike any other natural estrogen. E4 was first described in 1965 by Diczfalusy and co-workers of the Karolinska Institute in Sweden. An abundance of studies has shown that E4, like all estrogens, binds to two subpopulations of the estrogen receptor alpha (ERα): the nuclear ERα which induces gene transcription and the membrane ERα which initiates rapid signalling. Like other estrogens, E4 activates the nuclear ERα and induces gene transcription. However, in contrast to other estrogens, E4 antagonises the activity of the membrane ERα. This property of E4 is the basis for its tissue selectivity and its unique clinical profile. As a result, E4 has contraceptive properties while displaying minimal impact on steroid- and drug-metabolizing liver enzymes, suggesting a lower impact on haemostasis and lipids compared to other estrogens.
Diczfalusy et al. failed to demonstrate the clinical usefulness of E4 plasma levels as a diagnostic tool assessing the fetal status. In 2001, Herjan Coelingh Bennink in the Netherlands suggested the therapeutic potential of E4 and started the E4 clinical development programme. Phase 1 studies showed that E4 is efficiently absorbed with oral administration, has a half-life much longer than other natural estrogens, and rapidly achieves stable therapeutic blood concentrations with oral administration. Phase 2 clinical trial data have demonstrated the unique potential benefits of a combination of E4 15 mg with DRSP 3 mg as a combined oral contraceptive. Based on the promising phase 2 data demonstrating high efficacy and tolerability and a minimal impact on haemostasis and metabolic parameters, Mithra Pharmaceuticals embarked on the endeavour to develop E4/DRSP further. A full phase 3 programme was started in 2015 in Europe and Russia, the US and Canada to evaluate E4 in combination with drospirenone. In 2019, the results of two large phase 3 trials confirmed the high contraceptive efficacy, good tolerability and absence of unexpected adverse events. It is expected that this combined oral contraceptive, with its unique benefit/risk profile, will be available soon to women and clinicians seeking new contraceptive options.

E4 - It is time for a Renaissance in Oral Contraception (REn4issance) (sponsored by Gedeon Richter and Mithra Pharmaceuticals)

Restoring faith in COC: an important haemostasis update

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Combined oral contraceptives (COC) containing ethinyl estradiol (EE) increase the synthesis of coagulation factors and decrease the levels of several anticoagulant factors, and thereby lead to an increased risk of venous thromboembolism (VTE). To minimize COC impact on VTE risk, new estrogens with less impact on the liver and the synthesis of coagulation factors are an important breakthrough.

In 2005, the European Medicines Agency recommended that biological variables possibly related to VTE risk should be investigated during drug development. However, which biomarkers are associated with VTE risk remains unclear. Changes in plasma levels of antithrombin, (free)-protein S, free-TFPI, prothrombin, factor VIII, and fibrinogen are relevant parameters for relating VTE risk and hormone therapy for contraception.

Furthermore, the endogenous thrombin potential based activated protein C (ETP-based APC) resistance test, expressed as normalized APC sensitivity ratio (nAPCsr), is a global test sensitive to all coagulation defects recognized individually as prothrombotic factors. The ETP-based APC resistance test may provide insight on the risk of VTE.

In women receiving E4 15mg /drospirenone (DRSP) 3mg for 6 consecutive treatment cycles of 28 days, a similar 30% increase of the ETP-based nAPCsr was observed while changes with EE 20μg/DRSP 3mg and EE 30μg/LNG 150μg were 219% and 165%, respectively. E4/DRSP also displayed a lower impact on other procoagulant parameters such as free protein S, tissue plasminogen activator and prothrombin fragment 1+2 than the combination of EE/LNG or EE/DRSP. The differences noted between E4/DRSP and EE/DRSP, products that contain the same amount of DRSP with different estrogens, confirms the importance of the estrogen choice in a COC. These data clearly show that the hypercoagulable effect of COCs are mainly mediated by the estrogenic component. E4 should be considered as a breakthrough molecule for the next generation of COC.

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It is time for a Renaissance in Oral Contraception (REn4issance): revitalising women's choice for a COC

Carolyn Westhoff (US)
Columbia University

Choosing an oral contraceptive is influenced by many factors, including efficacy, side effects, bleeding profiles, clotting risk, ease of use, changes in sexual function, costs, personal experiences, perceptions of how a contraceptive may impact quality of life (QoL) and the balance between all these factors.
In the clinical development programme of the combined oral contraceptive (COC), estetrol (E4) 15mg combined with drospirenone (DRSP) 3mg, many of these factors have been studied.
A phase 2 study evaluated the efficacy of E4 15mg/DRSP 3mg to suppress ovarian function compared to ethinyl estradiol (EE) 20μg/DRSP 3mg COC. Ovarian function, reflected by Hoogland score, showed adequate suppression in both treatment groups.
An additional phase 2 randomized open-label study assessed the impact of E4 15mg/DRSP 3mg on haemostasis, endocrine and metabolic parameters. Healthy women of reproductive age received E4 15mg/DRSP 3mg (n=34), EE 30μg/ levonorgestrel (LNG) 150μg (n=25), or EE 20μg/DRSP 3mg (n=29). Individual measurements of coagulation factors associated with venous thromboembolism (VTE) risk showed no significant changes from baseline to cycle 6 in E4/DRSP treatment group, while significant changes were noted in EE/LNG and EE/DRSP across various parameters. Factors assessed included fibrinogen, prothrombin, Factors VII and VIII, von Willebrand factor, antithrombin, protein S free, protein S activity, tissue factor pathway inhibitor (TFPI) free, protein C, plasminogen, plasminogen activator inhibitor-1, tissue plasminogen activator, D-dimer, prothrombin fragment 1+2 and ETP-based nAPCsr. Liver proteins (CBG, SHBG, TBG, and angiotensinogen) increased to a lesser extent with E4/DRSP. E4/DRSP treatment showed minimal impact on lipid parameters, similar to EE/DRSP treatment. However, E4/DRSP showed no increase in triglycerides as was seen with EE/LNG. Carbohydrate metabolism was not impacted.
QoL is a key component of subject adherence to treatment. In another trial, E4 15mg /DRSP 3mg usage was associated with high-user acceptability, satisfaction, and willingness to use the new COC in the future.
E4/DRSP effectively suppresses ovarian function, offers high user satisfaction and acceptability, has lower impact on haemostatic and lipid parameters than other COCs and negligible impact on carbohydrate metabolism. These data suggest E4/DRSP may offer less cardiovascular disease risk, and less residual VTE risk than other COCs, in particular EE/DRSP.

E4 - It is time for a Renaissance in Oral Contraception (REn4issance) (sponsored by Gedeon Richter and Mithra Pharmaceuticals)

It is time for a Renaissance in Oral Contraception (REn4issance): bringing this renaissance to life: phase III results

Mitchell Creinin (US)
University of California

After successful completion of phase 2 trials with E4 15mg /DRSP 3mg (E4/DRSP, 24/4-day regimen), two phase 3 open-label non-comparative trials were performed in Europe/Russia (EU/RUS) and US/Canada (US/CAN) to confirm the contraceptive efficacy and safety of this new combined oral contraceptive (COC).
The EU/RUS trial enrolled women 18-50 years at 69 European and 10 Russian sites. The US/CAN trial enrolled women 16-50 years at 70 US and 7 Canadian sites. In total, 1,553 women in EU/RUS and 1,864 women in US/CAN initiated treatment.
The primary contraceptive efficacy endpoint was measured in women 35 years and younger at screening, with Pearl Index of 0.44 (95% CI 0.14-1.03) in the EU/RUS trial and 2.65 (95% CI 1.73-3.88) in the US/CAN trial. Mean percentage of women reporting intracyclic bleeding over 13 cycles was 16% in EU/RUS and 19.5% in US/CAN; majority of which was classified as spotting. The mean percentage of women with no scheduled bleeding/spotting across all cycles was 7.9% (EU/RUS) and 16.0% (US/CAN). Unscheduled bleeding/spotting decreased when evaluating rates at cycles 1, 2, 6 and 12 (EU/RUS: 23.5%, 19.2%, 15.6% and 13.0%, respectively; US/CAN: 30.3%, 21.8%,19.2% and 17.4%, respectively). Discontinuation for bleeding complaints in the EU/RUS and US/CAN trials occurred in 3.1% and 4.7%, respectively. Tolerability for E4/DRSP in the two trials was excellent; no unexpected safety concerns were identified.
In EU/RUS trial, 77.0% of women completed 13 cycles of use, compared to 54.5% in the US/CAN trial. The most common reasons for discontinuation in the EU/RUS trial were AEs unrelated to bleeding (6.4%), consent withdrawal (4.9%), AEs related to bleeding (3.1%), and protocol deviations (0.8%). In the US/CAN trial, these reasons were lost to follow up (15.5%), consent withdrawal (7.3%), AEs unrelated to bleeding (4.7%), and protocol deviations (4.3%).
Quality of life (QoL) evaluations using the Menstrual Distress Questionnaire Cycle (MDQc) demonstrated a decrease in cramps, painful and tender breasts in the menstrual phase relative to baseline. In the pre-menstrual phase, there were fewer women reporting complaints of skin blemishes/disorders, mood swings, irritability, and crying relative to baseline.
Overall E4/DRSP demonstrates high efficacy with a regular bleeding pattern and minimal unscheduled bleeding for most users. QoL evaluations demonstrated changes consistent with other oral contraceptives. EMA and FDA filing are ongoing.

Maternal Nutrition and Pregnancy Outcomes (sponsored by P&G Health Germany)

What's the role of vitamin D for fertility, pregnancy and lactation?

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Medical University of Graz

Vitamin D exerts its biological actions by binding to vitamin D receptors (VDRs) that are expressed in almost all tissues and that regulate the expression of hundreds of genes. This classic function as a steroid hormone along with the increased activity of vitamin D metabolism during pregnancy and the total dependence of the fetus of mothers' vitamin D status provide a sound scientific rationale for a critical role of vitamin D during preconception, pregnancy, and lactation. Epidemiological studies indicate that vitamin D deficiency is a risk marker for reduced fertility and various adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes mellitus, preterm birth, and low birth weight. Randomized controlled trials (RCTs) and meta-analyses of RCTs have partially, but not consistently, documented that vitamin D supplementation reduces these adverse pregnancy outcomes. An important outcome of published trial data is that vitamin D supplementation during pregnancy is safe. While there are still some knowledge gaps with regard to vitamin D supplementation and extra-skeletal health outcomes, there are established effects of vitamin D for the prevention and treatment of musculoskeletal diseases, in particular regarding rickets and osteomalacia. Dietary reference intakes are based on these latter outcomes, but there exists a huge gap between recommended vitamin D intakes and the high prevalence of vitamin D deficiency in the general population including pregnant women. With reference to routine clinical practice, a daily vitamin D intake of about 800 to 1000 international units (20μg to 25 μg) per day is safe and sufficient to meet vitamin D requirements during preconception and pregnancy as recommended by nutritional vitamin D guidelines.

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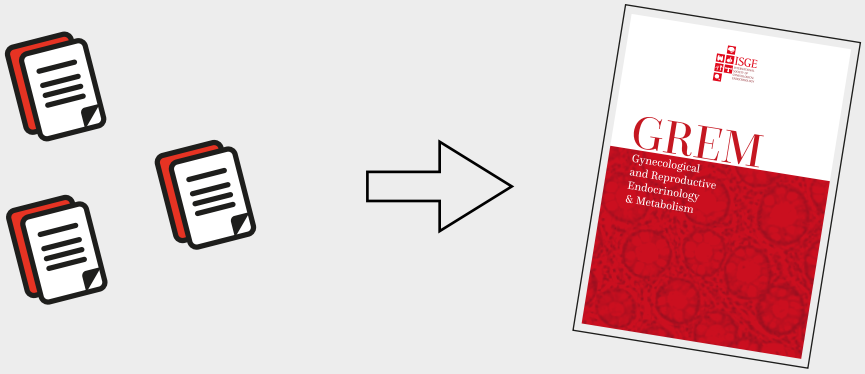

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