MedCrave
Step into the World of Research

MOJ Anatomy & Physiology

Research Article

Open Access

CrossMark

Structural changes in the uterine artery of the domestic pig (*Sus scrofa domesticus*) in the first trimester of pregnancy

Abstract

Background: Adaptation of the uterine artery in pregnancy involves changes in anatomy that include widening of the lumen, medial thickening, elastic lamina degradation, and smooth muscle cell hypertrophy. Early remodeling of the uterine vascular system is needed to maintain pregnancy and ensure desired pregnancy outcome. The trigger mechanisms for uterine artery remodeling are uncertain. Also unclear are the regional variations in the uterine artery in the first trimester of pregnancy.

Methods: 10 domestic pigs (Sus scrofa) 5 in the first trimester of pregnancy and 5 non gravid were sacrificed to examine the structure of the uterine artery. The specimens were prepared for paraffin wax embedding and stained with Masson's Trichrome, Weigert's Resorcin-Fuschscin counterstained with Van Gieson stain and Hematoxylin and Eosin. Slides were examined with a light microscope at x40, x100, and X400 magnification. Observations made were recorded and photomicrographs taken.

Results: The Uterine artery of the domestic pig in the first trimester showed marked reduction in the thickness of the tunica intima, a prominent internal elastic lamina and elastic fibres. The tunica media had hypertrophied vascular smooth muscle with zonation of the media into inner circular and outer longitudinal smooth muscle layers in the proximal regions of the artery. There was also prominence of the Vasa vasorum in the adventitia of these uterine arteries that reduced distally along the artery.

Conclusion: The proximal sections of the uterine artery shows unique physical-mechanical adaptation in the first trimester of pregnancy related to increased demand of blood to the feto-placental unit.

Keywords: vasoactive substances, paraffin wax, non-gravid uterine artery, smooth muscles, artery, female sex steroids

Volume 6 Issue 4 - 2019

Moses M Obimbo,[1,2] Anne Pulei,[1,2] Charles Omwandho,[3] Julius A Ogeng'o[1]

[1]Department of Human Anatomy, University of Nairobi, Kenya
[2]Department of Obstetrics and Gynecology, University of Nairobi, Kenya
[3]Kirinyaga University, Kenya

Correspondence: Moses M Obimbo, Department of Human Anatomy, Department of Obstetrics and Gynecology, University of Nairobi, Kenya,
Email obimbomad@gmail.com, moses.obimbo@uonbi.ac.ke, moses.madadi@ucsf.edu

Received: June 24, 2019 | **Published:** July 12, 2019

Abbreviations: TUA, terminal uterine artery; TCE, trichloroethane; IEL, internal elastic lamina; eNOS, endothelium nitric oxide sythetase; nNOS, neuronal NOS

Introduction

The gravid and nongravid uterus receive blood supply from the paired uterine arteries and uterine branches of the ovarian arteries. These arteries anastomose giving rise to arcuate arteries which enter the myometrium to form the radial arteries and finally the spiral arteries within the decidua. In normal pregnancy, there are multiple physiological changes that take place to nurture the developing fetus. Maternal cardiovascular system, for example, undergoes adaptation such as a fall in systemic vascular resistance with dramatic increase in uterine blood flow to meet the fetal metabolic demands.[1,2]

In early pregnancy, the endovascular trophoblast invade the inner third of the uterus and the spiral arteries converting them into large caliber channels that are well adapted for the uteroplacental exchange.[3,4] Thus presumably, in a normal pregnancy, the limiting factor to the uteroplacental blood flow would be upstream within the conduit vessels.

Adaptation of the uterine artery in pregnancy involves changes in both histology and morphometry that include widening of the lumen, media thickening, elastic lamina degradation, and smooth muscle cell hypertrophy which reverse after the termination of the pregnancy.[5,6] Early remodeling of the uterine vascular system contributes to the increased blood flow.[7] Since the change in the uterine blood flow occurs after vessel remodeling, there is need to maintain this state throughout the pregnancy. The trigger mechanisms for uterine artery remodeling are unclear. Several mechanisms have been proposed including, mechanical force exerted by increased blood flow,[8,9] increased level of circulatory vasoactive substances,[10] the conceptus and effect of estrogen acting through estrogen receptors have been suggested.[11–13] In complicated pregnancies such as diabetes, preeclampsia, obesity, there is inadequate remodeling of the uterine arteries which may lead to uterine artery dysfunction impairing the fetal growth and development.[14–16]

It is unclear whether there are regional variations in the adaptation of the uterine artery in the first trimester of pregnancy and what the changes (if any) would imply.

Methods

A total of 10 domestic pigs (*Sus scrofa*) 5 in the first trimester of pregnancy (less than 1 month 1 week in pregnancy) and 5 non gravid were sacrificed to examine the structure of the uterine artery. Only animals that were verified to be healthy by a veterinary doctor and

did not have any recognizable cardiovascular disease were included in this study.

After weighing the pigs, they were anesthetized with sodium pentobarbital (50mg/kg IV) intravenously. With complete immobilization the animals were opened through a mid-line abdominal incision and thoracotomy to expose the heart. For complete clearance of blood, a canula were inserted into the left ventricle and saline, introduced from the perfusion kit 1.5metres above the heart and the right auricle punctured to drain out the blood followed by 10% formaldehyde solution perfused for 30 minutes using gravitational trans-cardiac perfusion kit.

The aorta, common iliac, internal iliac and uterine artery were identified sequentially. The uterine artery was dissected in three parts; the segment just after the internal iliac artery named main trunk uterine artery (MTUA), A. The segment within the broad ligament named broad ligament uterine artery (BLUA), B and the terminal part named terminal uterine artery (TUA), C.

The specimens were fixed in 10% formaldehyde solution and dehydrated in increasing concentrations of alcohol of 70% to absolute alcohol each for one hour. They were prepared for paraffin wax embedding by clearing in Trichloroethane (TCE) for two hours and infiltrated with wax for 12 hours. They were then embedded in fresh molten wax for 12hours. Seven micrometer thin serial sections were cut using a Leitz Wetzlar sledge microtome, floated in warm water and thereafter mounted and then dried in hot air oven at 40°C overnight.

The sections were stained with Masson's Trichrome and Hematoxylin and Eosin. Slides were examined under Leica Light microscope at x40, x100 and x400 magnification. Observations made were recorded on the preformatted data sheet and photomicrographs taken.

Results

During the first trimester pregnancy, the tunica intima reduced in thickness compared to the tunica intima from a uterine artery of a non-gravid uterus (Figure 1A & 1B). The tunica intima was composed of the endothelium, the subendothelial layer and a prominent, continuous but folded internal elastic lamina with some areas of duplication (Figure 1C). The endothelial cells were cuboidal in shape and exhibited prominent nucleus (Figure 1D). There was a marked reduction in thickness of the subendothelial layer and the fibromusculoelastic content were poorly discernible.

The tunica media was prominent with enlarged and elongated circular smooth muscles with prominent longitudinal muscle fibre bundles (Figure 1E) and reduced volume of collagen fibres but increased amount of elastic fibres (Figure 1C) compared to non-gravid uterine artery. The elastic fibres were interspersed within the elongated smooth muscles.

The tunica adventitia was composed of collagen fibres loosely and circumferentially arranged. Vasa vasora in the adventitia were more prominent than in non-gravid uterine artery (Figure 1F). These changes were consistent within the main trunk and broad ligament segments. The terminal segment had all the other features seen in the MTUA and BLUA except that the tunica media was composed of only circular smooth muscles and lacked longitudinal bundle seen in the other segments.

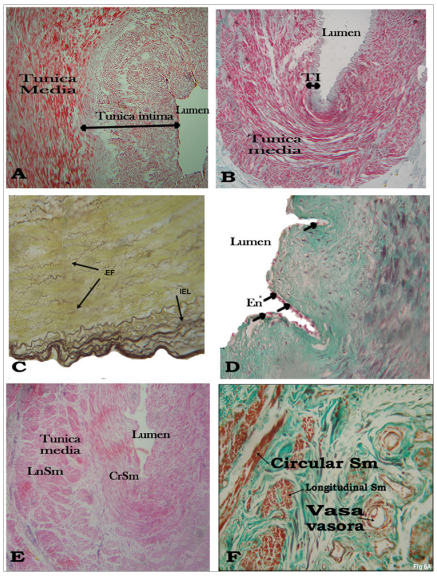

Figure 1 Histology of the uterine artery of the domestic pig during the first trimester pregnancy. The uterine arteries biopsies were taken from three regions of the uterine artery the main trunk (MTUA), the broad ligament (BLUA) and the terminal segment (TUA) then prepared for paraffin wax embedding, sectioned and stained with either Hematoxylin & Eosin, Masson Trichrome stains or Weigert's Resorcin-Fuschscin conterstained with Van Gieson stain.

(A) Uterine artery from a non-gravid adult domestic pig used for comparison purposes. Note the tunica intima showing a thickened morphology, X100.

(B) Main trunk uterine artery in the 1st trimester pregnancy. Notice the thickness of the tunica intima, TI, markedly reduced compared to A. Note also the prominent internal elastic lamina, X100.

(C) Main trunk uterine artery showing tunica intima and media. Note the prominent internal elastic lamina, IEL and elastic fibres, EF in the media., X100.

(D) Broad ligament uterine artery showing the endothelial cells, (En). Notice that their shape varies from squamous to cuboidal, X100.

(E) Tunica media of main trunk uterine artery. Notice the zonation of the media into inner circular, (CrSm) and outer longitudinal smooth muscle, (LnSm) layers, X100.

(F) Tunica adventitia of broad ligament segment of uterine artery. Note the prominent vasa vasora in the adventitia, X400.

Citation: Obimbo MM, Pulei A, Omwandho C, et al. Structural changes in the uterine artery of the domestic pig (*Sus scrofa domesticus*) in the first trimester of pregnancy. *MOJ Anat & Physiol.* 2019;6(4):112–115. DOI: 10.15406/mojap.2019.06.00256

Discussion

The tunica intima was markedly reduced in thickness compared to uterine artery from a non-gravid uterus with distinct endothelium, the subendothelial layer and a prominent, continuous and folded internal elastic lamina with some areas of duplication. This was more marked in the proximal section of the uterine artery. The reduction in intimal thickness has been described before and could be due to exposure to high quantities of circulating estrogen[17–20] and increased volume of blood flowing through the artery.[21–23] These factors are said to inhibit intimal hyperplasia. Indeed, it has long been postulated that sex of an individual has a role in the development of intimal hyperplasia with a greater female resistance. This has been attributed to direct or indirect beneficial effect of the female sex steroids.[24,25]

The Internal elastic lamina (IEL) represents a flexible barrier between the endothelium and tunica media and may have a role in physical barrier properties. It also allows for communication between the endothelium and the smooth muscle cell layers of the uterine artery through vasoactive substances and direct structural interaction.[26,27] The increased prominence of the internal elastic lamina is at variance with previous reports that suggest that internal elastic lamina degenerates during pregnancy.[28] The IEL has also been suggested to play a role in modulating smooth muscle cell migration from the media to the intima. For such smooth muscle cell migration to occur, it has been suggested that IEL fenestrations must be greater than 3–4µm wide. A prominent internal elastic lamina as observed in this case may be in part designed to provide increased mechanical strength to withstand the force of increased blood volume during the first trimester of pregnancy and may also explain the reduced intimal thickness of the intima during pregnancy.[29]

We observed that the smooth muscle cells were elongated, prominent and with multiple nuclei. There is insufficient information on the mechanism of medial remodeling during pregnancy. Some factors have been implicated including mechanical forces due to blood flow, increased levels of circulating vasoactive substances, higher amount of nitrous oxide and estrogen.[30–32] The elongation of the smooth muscle cells results from the direct effect of the endothelium nitric oxide sythetase (eNOS) and cell hypertrophy.[33] In addition, the neuronal NOS (nNOS) also causes outward remodeling of the media leading to vascular smooth muscle hypertrophy.[34]

The increase in the number and sizes of the vasa vasorum is in keeping with increased demand of oxygen and nutrition to the hyperplastic and hypertrophied tunica media. This is similar to other reports.[35–37] Failure of the uterine vessels to properly adapt may lead to uterine artery dysfunction marked by increased vessel resistance to blood flow to the feto-placental unit. The consequences may involve fetal intrauterine growth restriction and other undesired pregnancy outcomes.

In conclusion, the proximal sections of the uterine artery shows unique physical-mechanical adaptation in the first trimester of pregnancy related to increased demand of blood to the feto-placental unit.

Acknowledgments

None.

Conflicts of interest

The authors declare there are no conflicts of interest.

References

1. Thaler I, Manor D, Itskovitz J, et al. Changes in uterine blood flow during human pregnancy. *Am J Obstet Gynecol*. 1990;162(1):121–125.
2. Bird IM, Zhang L, Magness RR. Possible mechanisms underlying pregnancy-induced changes in uterine artery endothelial function. *Am J Physiol Regul Integr Comp Physiol*. 2003;284(2):R245–R258.
3. Gerretsen G, Huisjes, HJ, Elema, JD. Morphological changes of the spiral arteries in the placentae bed in relation to pre-eclampsia and fetal growth retardation. *Br J Obstet Gynaecol*. 1981;88(9):876–881.
4. Craven CM, Morgan T, Ward K. Decidual spiral artery remodelling begins before cellular interaction with cytotrophoblasts *Placenta*. 1998;19(4):241–252.
5. van der Heijden OWH, Essers YP, Fazzi G, et al. Uterine artery remodeling and reproductive performance are impaired in endothelial nitric oxide synthase-deficient mice. *Biol Reprod*. 2005;72(5):1161–1168.
6. Obimbo MM, Omwandho C, Ogeng'o JA. Regional differences in the tunica media of the uterine artery of domestic pig (*Sus scrofa domesticus*): basis for uterine blood flow. *Anatomy Journal of Africa*. 2015;4(1):505–511.
7. Osol G, Moore LG. Maternal uterine vascular remodeling during pregnancy. *Physiology (Bethesda)*. 2009;24:58–71.
8. van der Heijden OW, Essers YP, Spaanderman ME, et al. Uterine artery remodeling in pseudopregnancy is comparable to that in early pregnancy. *Biol Reprod*. 2005;73(6):1289–1293.
9. Jorge S, Chang S, Barzilai JJ, et al. Mechanical signaling in reproductive tissues: mechanisms and importance. *Reprod Sci*. 2014;21(9):1093–1107.
10. Dechanet C, Fort A, Barbero-Camps E, et al. Endothelin-dependent vasoconstriction in human uterine artery: application to Preeclampsia. *PLoS One*. 2011;6(1):e16540.
11. Sprague BJ, Phernetton TM, Magness RR, et al. The effects of the ovarian cycle and pregnancy on uterine vascular impedance and uterine artery mechanics. *Eur J Obstet Gynecol Reprod Biol*. 2009;144 Suppl 1:S170–S178.
12. Mandala M, Osol G. Physiological remodelling of the maternal uterine circulation during pregnancy. *Basic Clin Pharmacol Toxicol*. 2012;110(1):12–18.
13. Obimbo MM, Omwandho C, Ogeng'o JA. Correlation between morphometry of the uterine artery and estradiol levels in non pregnant domestic pigs (*Sus scrofa domesticus*). *JOGECA*. 2013;25(1):23–28.
14. Phillips JK, Vance AM, Raj RS, et al. Impact of experimental diabetes on the maternal uterine vascular remodeling during rat pregnancy. *Reprod Sci*. 2012;19(3):322–331.
15. Spradley FT, Palei AC, Granger JP. Immune mechanisms linking obesity and preeclampsia. *Biomolecules*. 2015;5(4):3142–3176.
16. Goulopoulou S. Maternal vascular physiology in preeclampsia. *Hypertension*. 2017;70(6):1066–1073.
17. Mendelsohn ME. Estrogen actions in the cardiovascular system. *Climacteric*. 2009;12 Suppl 1:18–21.
18. Murphy E. Estrogen signaling and cardiovascular disease. *Circ Res*. 2011;109(6):687–696.
19. Reslan OM. Khalil RA. Vascular effects of estrogenic menopausal hormone therapy. *Rev Recent Clin Trials*. 2012;7(1):47–70.
20. Usselman CW, Stachenfeld NS, Bender JR. The molecular actions of oestrogen in the regulation of vascular health. *Exp Physiol*. 2016;101(3):356–361.

21. Pries AR, Reglin B, Secomb TW. Remodeling of blood vessels: Responses of diameter and wall thickness to hemodynamic and metabolic stimuli. *Hypertension*. 2005;46(4):725–731.

22. Bartoli CR, Spence PA, Siess T, et al. Nonphysiologic blood flow triggers endothelial and arterial remodeling *in vivo*: Implications for novel left ventricular assist devices with a peripheral anastomosis. *J Thorac Cardiovasc Surg*. 2014;148(1):311–321.

23. Green DJ, Hopman MT, Padilla J, et al. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiol Rev*. 2017;97(2):495–528.

24. Westendorp IC, in 't Veld BA, Bots ML, et al. Hormone replacement therapy and intima-media thickness of the common carotid artery: The Rotterdam study. *Stroke*. 1999;30(12):2562–2567.

25. Chan YX, Knuiman MW, Hung J, et al. Testosterone, dihydrotestosterone and estradiol are differentially associated with carotid intima-media thickness and the presence of carotid plaque in men with and without coronary artery disease. *Endocr J*. 2015;62(9):777–786.

26. Dees MB. On the fenestrated membrane of henle. *The Anatomical Record*. 1923;26(2):161.

27. Masuda H, Zhuang YJ, Singh TM, et al. Adaptive remodeling of internal elastic lamina and endothelial lining during flow-induced arterial enlargement. *Arterioscler Thromb Vasc Biol*. 1999;19(10):2298–2307.

28. Miyagi M. Studies on the change in uterine artery media of cows caused by pregnancy. *Sci Bull Coll Agri University Ryukyus*. 1966;13:1–9.

29. Sims FH. Discontinuities in the internal elastic lamina: a comparison of coronary and internal mammary arteries. *Artery*. 1985;13(3):127–143.

30. Lu D. Kassab, GS. Role of shear stress and stretch in vascular mechanobiology. *JR Soc Interface*. 2011;8(63):1379–1385.

31. Resanovic I, Rizzo M, Zafirovic S, et al. Anti-atherogenic effects of 17β-estradiol. *Horm Metab Res*. 2013;45(10):701–708.

32. Zhao Y, Vanhoutte PM, Leung SWS. Vascular nitric oxide: Beyond eNOS. *J Pharmacol Sci*. 2015;129(2):83–94.

33. Cipolla M, Osol G. Hypertrophic and hyperplastic effects of pregnancy on the rat uterine arterial wall. *Am J Obstet Gynecol*. 1994;171(3):805–811.

34. Tronc F, Mallat Z, Lehoux S, et al. Role of matrix metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arterioscler Thromb Vasc Biol*. 2000;20(12):E120–E126.

35. Zezula-Szpyra A, Gawronska B, Skipor J. Vasa vasorum of blood and lymph vessels in the broad ligament of the sheep uterus analyzed by scanning electron microscopy. *Rocz Akad Med Bialymst*. 1997;42:134–146.

36. Cicinelli E, Einer-Jensen N, Galantino P, et al. The vascular cast of the human uterus: from anatomy to physiology. *Ann N Y Acad Sci*. 2004;1034:19–26.

37. Mulligan-Kehoe MJ. The vasa vasorum in diseased and nondiseased arteries. *Am J Physiol Heart Circ Physiol*. 2010;298(2):H295–H305.

Citation: Obimbo MM, Pulei A, Omwandho C, et al. Structural changes in the uterine artery of the domestic pig (*Sus scrofa domesticus*) in the first trimester of pregnancy. *MOJ Anat & Physiol.* 2019;6(4):112–115. DOI: 10.15406/mojap.2019.06.00256