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REVIEW

Charles O. A. Omwandho · Susanne E. M. Gruessner
Hans-R Tinneberg

Early pregnancy loss and neonatal deaths associated with Klebsiella pneumonia infection: a mini review of possible occupational health risk

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Abstract Recurrent pregnancy loss is a disease of grave psychological and economic concern. The etiology in the vast majority of the cases is unknown or at best poorly understood. Although Klebsiella pneumonia infections have been reported in humans and animals during pregnancy, there is hardly any information to indicate whether or not these infections may be responsible for early pregnancy loss. We present a review of literature and report for the first time in humans, Klebsiella pneumonia infection in placenta of a 38-year-old secondary recurrent aborter (parity 2 + 3).

Keywords Pregnancy · Recurrent spontaneous abortion · Klebsiella pneumonia

Introduction

Abortion in humans is defined as the damage and death of an embryo accompanied by the onset of uterine contractions (labor) and its subsequent expulsion from the body and recurrent abortion the loss of three or more consecutive pregnancies before 20 weeks of gestation. Abortion is referred to as primary if the woman has never had a live birth previously and secondary if she has. Missed abortion occurs when there is failure to expel the fetus after intrauterine death.

Recurrent pregnancy loss (RPL) occurs in 1–2% of the childbearing population [1]. The mechanisms involved are not well understood in humans but are often likened to what has been observed in laboratory animals. This condition is thought to result from a number of factors including genetic [2, 3], anatomical [4, 5], endocrine [4, 6], immunological [7, 8], placental anomalies [9, 10], behavioral factors such as smoking and alcohol consumption [11], as well as exposure to lead, mercury, ethylene oxide, and ionizing radiation [12] among others. Epidemiological studies suggest that the risk of subsequent pregnancy loss is approximately 24% after two clinical pregnancy losses, 30% after three and 40% after four consecutive spontaneous abortions [13, 14]. Given the psychological and economic stresses associated with RPL, there is a need to investigate and fully understand the mechanisms involved with the view to developing effective therapy.

C. O. A. Omwandho
Department of Biochemistry, University of Nairobi,
P.O. Box 30197, Nairobi, Kenya

S. E. M. Gruessner · Hans-R Tinneberg (✉)
Frauenklinik, Universitätsklinikum Giessen,
Klinikstrasse 28, 35385 Giessen, Germany
E-mail: Hans-Rudolf.Tinneberg@gyn.med.uni-giessen.de

Klebsiella pneumonia infections in pregnancy

Klebsiella pneumonia infections have been reported in pregnancy and in association with neonatal deaths. However, there are hardly any reports to indicate whether or not these infections may be associated with premature loss of pregnancy. In cases where there is pregnancy loss, it is equally difficult to determine whether or not such infections would be the cause or a consequence of intrauterine infection and early fetal demise. In one case, a retrospective study was conducted to determine epidemiology of neonatal bacterial infection and to evaluate the efficacy of antibiotic protocols used at the University teaching Hospital in Dakar, Senegal [15]. The authors reported that premature rupture of membranes accounted for 85% of the risks during pregnancy. Also 246 newborns (about 33 per 1,000 new borns) had bacterial infections with Klebsiella pneumonia accounting for 61.5% of the total neonatal bacterial infections and 79% of neonatal deaths. It was not established whether or not there may have been a link between premature rupture of membranes and Klebsiella pneumonia infections. In a related case, Klebsiella pneumonia infection was demonstrated in a fluid aspirated from a myoma in a 44-year-old woman in the 26th week of gestation [16]. Elsewhere, a major outbreak of clinical infections was caused by multiresistant

Klebsiella pneumonia in the neonatal ward of the Maternite Wassila Bourguiba Hospital in Tunis, Tunisia in 1996 [17]. Klebsiella pneumonia has also been reported in the placenta of horses following septic abortions [18] but it was not established whether or not the abortion may have been the cause or a consequence of Klebsiella pneumonia infection. An interesting report implicated an imported carrier stallion from Europe in causing an extensive outbreak of equine viral arteritis (EVA) through seminal contamination on a Warmblood breeding farm in Pennsylvania USA [19]. In this study, strains of equine arteritis virus (EAV) present in semen of two carrier stallions (A and G) on the farm were compared with those in tissues of foals born during the outbreak. Nucleotide and phylogenetic analyses confirmed that the viruses present in semen of stallion A initiated the outbreak. However, virus in the placenta of one foal differed by one nucleotide (99.9% identity) from the predominant outbreak virus. These results confirmed that EVA can be initiated by horizontal aerosol transmission of viruses in semen of carrier stallions.

A clinical history of Klebsiella pneumonia infection

Klebsiella pneumonia infections have not been associated with pregnancy loss in humans previously. However, we encountered a 38-year-old health worker (parity 2 + 3) who had delivered two healthy baby boys in 1991 and 1993 with no complications before the onset of RPL. Subsequent pregnancies were lost in the second trimester gestational weeks 21, 18 and 15, respectively, in 1996, 1998 and 1999. Preliminary investigations at our clinic showed no antibodies to cardiolipin, smooth muscles, thromboplastin, nuclear DANN, and Rhesus factor antigens. There was no evidence of hepatitis B antigens, HBs, TORCH or genetic abnormalities. On the basis of these observations, we assumed immunological etiology and admitted the patient to in vitro fertilization, IVF using ICSI and embryo transfer (ET). The pregnancy was conducted under antibiotic prophylaxis, therapy to enterococci, heparin and passive immunotherapy using intravenous immunoglobulin, IVIG. Beginning the 8–13th weeks of gestation, the patient was put on IVIG (16 g/week) plus oral dose of Folsäure (Lafol), vitamin B–K complex (Multibionet forte N) and 200 μg of iodide together with physical rest and restriction on caffeine intake. Routine investigations on the 11th week of gestation showed evidence of enterococcus in cervical smear but no signs of Chlamydia. A 10 day long therapy was initiated with Erythromycin according to resistogram sensitivity and a further 10 days with Amoxicillin together with local therapy using vagiflor supplement. On the 12th gestational week, there was light vaginal bleeding and we put the patient on bed rest to restrict further placental bleeding and heparin s.c (Mono-Embolex 0.3 ml) to limit embolism and maintain efficient placental perfusion. A regular ultrasound taken on 13th week showed normal development and no striking evidence of pathology. However, on the 15th week, there was sonographic evidence of intrauterine fetal death but no conspicuous sign of fetal size discrepancy.

The abortive placenta was immediately sent for pathological analysis and bacterial investigations. There was no evidence of pathology on the placenta but bacterial analysis showed Klebsiella pneumonia infection and many granulocytes with gram negative bacteria. Post mortem examination did not show evidence of pathology on the fetus. However, there were high titers of IgG antibodies to Herpes simplex virus, HSV (types 1 and 2) in fetal blood but since there was no evidence of pathology on the fetus, we suspected that these antibodies may have arisen from maternal circulation.

On the basis of these observations we suspected that the infection and subsequent abortion may have been caused by occupational health risk since the husband was at the time of the study a practicing pulmunologist exposed to the risk of infection from patients with pneumonia, had previously been diagnosed with Klebsiella pneumonia prostatitis and had labial herpes at the time of this pregnancy. Interestingly, a subsequent pregnancy performed using IVIG with strict monitoring and therapy to Klebsiella pneumonia with Erythromycin resulted in birth of a healthy baby girl. This observation confirms our suspicion that Klebsiella pneumonia may have been responsible for loss of pregnancy.

Seminal contamination as a possible cause of Klebsiella pneumonia infection

Exposure to pathological agents has been associated with pregnancy losses previously [11, 12]. That Klebsiella pneumonia was reported in the placenta of horses following septic abortions [15] supports a possible link of placental infection to loss of pregnancy. Although Klebsiella pneumonia infections have been reported during pregnancy in humans [15, 16], no reports so far have linked these infections with loss of pregnancies. However, a massive outbreak of Klebsiella pneumonia infection in the neonatal ward in a Tunisian hospital demonstrates the invasive nature of Klebsiella pneumonia and re-enforces the need for proper maintenance of antiseptic conditions in hospitals and ventilation in surgical facilities. Additional reports by Cisse et al. [15] of Klebsiella pneumonia infections in pregnancy and subsequent association with neonatal deaths raises the possibility that these infections may lead to premature loss of pregnancies. These observations together with our report of Klebsiella pneumonia infection in abortive placenta suggest that such infections may be responsible for some of the pathophysiology associated with loss of pregnancies by women experiencing RPL. Although one cannot rule out the possibility of infection due to contamination during IVF and ET in our case, available evidence suggests that abortion may have resulted from seminal contamination with Klebsiella pneumonia

during copulation between the husband and the wife sometime before the onset of the aborted pregnancies. The presence of Klebsiella pneumonia in high concentrations and the microscopic evidence of gram negative bacteria in placental preparations provides more support for this hypothesis. This thesis is attractive since the husband had previously been diagnosed with Klebsiella pneumonia prostatitis and that a subsequent attempt at pregnancy by the same couple, using IVIG and with strict monitoring and therapy to Klebsiella pneumonia with Erythromycin resulted in birth of a healthy baby girl 1 year after the last abortion. We suspect that initial infection of the endometrium may have resulted from seminal contamination with Klebsiella pneumonia sometime before the onset of pregnancy but pathology may have been restricted by maternal immune responses. However, the generalized down-regulation of maternal immune responses during pregnancy, would have made it easier for the bacteria to multiply faster and infect placental tissue resulting in premature fetal death and abortion.

Conclusion and recommendations

The data provided in this study and elsewhere suggest that Klebsiella pneumonia infection may lead to premature loss of pregnancies. On the basis of this assumption, and review of literature, we recommend that in all cases of infertility and especially after recurrent abortion, male partners should be stringently screened for seminal contamination and where microbial infection is suspected or evident, the sperm should not be used for IVF and insemination by natural copulation avoided. In such cases, low dose antibiotic administration should be considered before IVF and ET for women with a history of RPL. In addition, weekly or fortnightly throat, vaginal as well as cervical canal smears should be taken and cultured to assess microbial growth after successful conception by infertile couples and evidence of infection followed with appropriate antibiotic therapy. Also, given the invasive nature of Klebsiella pneumonia, it is advisable that antiseptic conditions and ventilation in hospitals and surgical facilities be well maintained in order to avoid possible disease outbreaks and occupational health risks.

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