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Viral Infections in Pregnancy: A Focus on Ebola Virus

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Abstract

During gestation, the immune response of the placenta to viruses and other pathogens plays an important role in determining a pregnant woman's vulnerability toward infectious diseases. Located at the maternal-fetal interface, trophoblast cells serve to minimize the spread of viruses between the host and developing fetus through an intricate system of innate antiviral immune signaling. Adverse pregnancy outcomes, ranging from learning disabilities to preterm birth and fetal death, are all documented results of a viral breach in the placental barrier. Viral infections during pregnancy can also be spread through blood and vaginal secretions, and during the post-natal period, via breast milk. Thus, even in the absence of vertical transmission of viral infection to the fetus, maternal health can still be compromised and threaten the pregnancy. The most common viral DNA isolates found in gestation are adenovirus, cytomegalovirus, and enterovirus. However, with the recent pandemic of Ebola virus, and the first documented case of a neonate to survive due to experimental therapies in 2017, it is becoming increasingly apparent that the changing roles and impacts of viral infection during pregnancy needs to be better understood, while strategies to minimize adverse pregnancy outcomes need to be identified. This review focuses on the adverse impacts of viral infection during gestation, with an emphasis on Ebola virus.

Keywords

Pregnancy; virus; neglected tropical diseases; placenta; ebola

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CONFLICT OF INTEREST

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DISCLAIMER

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

1. INTRODUCTION

In order to maintain a successful pregnancy, maternal immune tolerance toward the developing semi-allogenic fetus must exist. Any disturbances to this delicate balance could lead to deleterious consequences for both mother and fetus [1, 2]. It is the role of the innate immune system to identify “non-self infectious” agents such as bacteria and viruses, while promoting tolerance toward “non-infectious self”, which includes the mother, placenta, and fetus [3–7].

Intrauterine infection, whether bacterial or viral in nature, is strongly associated with adverse obstetrical outcomes such as pre-term labor, pre-eclampsia, and intrauterine growth restriction, though the mechanisms of these diseases remain incompletely understood [8, 9]. Microorganisms are capable of invading the amniotic cavity and causing pro-inflammatory changes in the chorioamniotic membranes, thus eliciting a pro-inflammatory response in the developing fetus. Hematogenous distributions via the placenta, and post-natally from breast milk are other ways in which infection can develop in the neonate [8, 10]. In fact, infection is one of the leading causes of preterm birth (PTB), and is the only pathological process for which there exists a direct causal link to prematurity, accounting for nearly 40% of occurrences [11].

It is important to note though, that not all viruses can be prevented from crossing the placental barrier. The acronym TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus (CMV) and Herpes), represents viral infections which have long been known to lead to adverse pregnancy outcomes and congenital defects [12–14]. In particular, CMV actually *inhibits* host cell autophagy, and may have evolved to cross the placental barrier in a manner more effective than other viruses [15]. In addition, certain retroviruses such as HIV make use of the same protein targeting and vesicle biogenesis pathways as exosomes. In doing so, these viruses avoid immune recognition in what is known as the “Trojan exosome” hypothesis [16].

Strong epidemiological evidence exists that the pregnant population is at increased risk of grave illness and mortality from viral infections [5, 17–21]. While guidelines are present to allow for the diagnosis of TORCH infections, there are currently no standards for the pre-natal management of other viral infections during pregnancy [19]. The recent pandemics of Ebola virus (EBOV) and Zika virus, which are linked to undesirable outcomes such as spontaneous miscarriage, fetal death, and microcephaly, have made it abundantly clear that the accurate and predictive management of viral disease during gestation is necessary [22–24]. This review will focus on EBOV history and transmission, its mechanisms of infection, and the impact that EBOV has on the community, maternal health, and fetal outcomes.

2. DISEASE HISTORY AND TRANSMISSION

EBOV, previously known as Ebola hemorrhagic fever, was first discovered in 1976 near the Ebola River, in what is currently known as the Democratic Republic of the Congo (DRC) [25]. While confirmed outbreaks of EBOV have since been reported and confined to sub-Saharan Africa, the 2014–2016 epidemic of EBOV is unmatched, having claimed over

11,000 lives, which exceeds more than two orders of magnitude across 29 previously documented outbreaks [26, 27]. In addition, over 5,000 of these cases occurred amongst women of reproductive age, which allowed for a rare opportunity to learn more about this virus in important sub-populations, such as pregnant and breastfeeding women [28, 29]. Centered in West Africa, the densest concentration of cases occurred in Guinea, Sierra Leone, and Liberia, though the virus also made its way to Europe and the United States of America [23, 30]. At the time of this outbreak, there were not any available treatments or vaccines, though a large number of clinical trials were eventually initiated [31].

Belonging to the virus family *Filoviridae*, genus *Ebolavirus*, there are 5 known EBOV species, which are negative-stranded, lipid enveloped RNA viruses [32]. *Zaire ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus* (formerly *Côte d'Ivoire ebolavirus)*, and *Bundibugyo ebolavirus* have all caused disease outbreak in humans, while *Reston ebolavirus* has only been known to cause disease outbreaks in non-human primates. It remains unknown how the patient first becomes infected at the start of an outbreak, though it is believed that fruit bats and nonhuman primates are the most likely reservoirs, thus classifying EBOV as a zoonotic disease [33].

The incubation period for EBOV is approximately 21 days (average 5–9 days). Though the mortality rate for EBOV is high in all age groups [case-fatality rate of approximately 50% (range: 25–90%)], it is highest in fetuses and neonates [30, 34]. Not contagious until symptoms appear, transmission of EBOV occurs via contact with the bodily fluids of people who are infected, including but not limited to urine, semen (including that of individuals who have recently recovered from the virus), saliva, sweat and breast milk. Contact with contaminated objects or animals such as needles, syringes, fruit bats and non-human primates, as well as contact with deceased victims, are other modes of transmission [35–37]. It still remains unclear if persistence of the virus has the ability to affect subsequent pregnancies in relation to birth defects, and undesired obstetrical outcomes.

The first several days of infection with EBOV are characterized by fever and non-specific symptoms such as fatigue, dyspepsia and headache, which then progress to vomiting, diarrhea, bleeding and abdominal pain. Due to the loss of gastrointestinal fluids and increased vascular permeability, patients may go on to develop shock, ultimately resulting in multiple organ failure and possibly death [33, 38, 39]. The clinical presentations of obstetrical complications and suspected Ebola infection, such as spontaneous miscarriage, intrauterine fetal death, vaginal bleeding, abdominal pain, chest pain, and fever, tend to have a large crossover [40].

The occurrences of pregnant women contracting EBOV are not isolated incidents, but rather, transpire as part of generalized transmission outbreaks within communities [23]. Being physically present at hospitals or doctors' offices for pre-natal appointments, and also by being caretakers in family units, can potentially increase the risk of exposure within the pregnant population [41]. In 2014, Mèdecìns Sans Frontières in Sierra Leone reported a decrease in pediatric and maternal clinic admissions, which was most likely due to the fear of contracting EBOV in a public setting [42].

Diagnosis of EBOV is based on clinical presentation or exposure history, and confirmed with diagnostic testing such as polymerase chain reaction (PCR), and IgM enzyme-linked immunosorbent assay (ELISA) in the early course of the disease, as well as oral swabs from cadavers [43, 44]. Viral antigen and nucleic acid can be detected in the blood starting as early as symptomatic day 1, and can continue to be detected all the way up until day 10 of symptomatic illness. Though viral RNA can be detected in some patients within 24 hours of symptom onset, a negative PCR result should not be used to rule out the presence of EBOV until 72 hours after symptoms begin [29, 45, 46].

Pregnant women that have obstetric and gynecological emergencies which require swift and invasive action can place healthcare workers at risk of exposure to bodily fluids. In these scenarios, life-saving interventions may be considered too dangerous to perform, due to the unknown EBOV status of the patients and the lack of appropriate protection for health staff [40, 47]. The use of finger stick blood sampling as opposed to venipuncture, and the oral swabbing of patients can potentially reduce the risk of EBOV exposure to healthcare workers [48].

As of March 2016, there were over 17,000 survivors of EBOV, with approximately 5,000 survivors having been women of child bearing age [49]. Presently, the specific pathophysiology of EBOV in pregnancy remains incompletely understood, with much of what we do know coming from previous outbreaks. Nearly all pregnancies in which the mother is infected will end with miscarriage or stillbirth [23]. Transmission is likely to occur *in utero*, since samples from amniotic fluid, placentas, and fetuses have all tested positive for EBOV, with the possibility of transmission also occurring during delivery and breastfeeding [35, 50, 51]. Data is still limited, however, on the clearance of EBOV from breast milk in convalescing women.

With the accumulation of findings on the benefits of human milk, which has been shown to significantly reduce incidences of neonatal necrotizing enterocolitis in infants weighing < 1500 g, and also to be more easily digested than cow milk-based formulas by infants with gastroschisis, the demand for donor human milk has been on the rise [52–54]. Most recently, Spence *et al.* reported that EBOV could not be detected by viral plaque assay in either donor human milk or culture media samples that were pasteurized using the Holder process. However, the virus will remain infectious in thawed, raw human milk at room temperature [55]. In areas where resources are limited, infants that are not breast-fed can be at increased risk of death from starvation and other infectious diseases [56].

3. EBOV AND THE PLACENTA

The human placenta, which has the key function of providing adequate nutrient and gas exchange between the mother and fetus, is responsible, in part, for the overall success of pregnancy, and a crucial regulator of embryonic and fetal development. Trophoblast cells, the major cell type of the placenta, appear as early as 3 days post-fertilization, and begin to produce human chorionic gonadotropin (hCG), the hormone responsible for ensuring that the environment of the endometrium is favorable to the implanting embryo [57]. These specialized epithelial cells are responsible for the cross-talk between the maternal and fetal

micro-environments and serve to limit the spread of contagions by immunologically defending the developing neonate [58, 59]. Defects in the proper formation of the maternal-fetal interface have been associated with complications of pregnancy [60].

In cases of EBOV infection involving pregnant women, sampling of the placenta allows for the opportunity to examine further the disease process and also to gain further insight into the mechanisms involved in vertical transmission. In cases where EBOV (*Sudan ebolavirus* and *Bundibugyo ebolavirus*) antigen has been detected *via* immunohistochemical analysis in both the syncytiotrophoblasts and cytotrophoblasts, this suggests that the virus can cross the placental epithelial barrier, thus resulting in transplacental infection of the fetus [61]. Interestingly, lymphocytes are the one cell type that have been shown to be resistant to EBOV infection [62].

Entry of EBOV into the cell is believed to occur via macropinocytosis and clathrin-mediated endocytosis, depending on the cell type. Classical clathrin mediated endocytotic vesicles are smaller than 200 nm in size and have been shown to internalize EBOV in HeLa cells, but not in Vero cells [63]. Nonetheless, both of these mechanisms are also essential for the placental acquisition of maternal nutrients for fetal growth [64]. In addition, the NPC1 gene, which is required for EBOV cellular infection, is also expressed on placental syncytiotrophoblasts [65].

Aside from EBOV entering cells via the same mechanisms that the placenta uses to acquire nutrients, EBOV has also been shown to evade humoral and cellular responses by encoding for multiple viral proteins which inhibit the synthesis and response of both of the Type 1 interferons (IFN) [66]. Type 1 IFNs are anti-viral proteins that are targeted by a number of viruses as a mechanism to evade immune recognition and cellular targeting, resulting in failure of both adaptive and innate immunity. Type 1 IFNs (IFN-1) are expressed on the placenta, and viral inhibition of the trophoblast IFN pathway has been shown to disable the regulation of the TLR-4 mediated pathway, thus promoting a pro-inflammatory repose to bacteria, and in mice, has been shown to lead to increased risk for PTB [67]. Discovery of this “double-hit” hypothesis by Racicot *et al.* could have implications in women that are simultaneously infected with EBOV and a bacterial infection, which could lead to PTB and other adverse pregnancy outcomes.

Delorme-Axford *et al.* have shown that trophoblasts are resistant to infection by a number of viruses and can further confer this resistance to non-placental recipient cells via the chromosome 19 microRNA cluster (C19MC miRNA). Expressed almost exclusively in the human placenta, C19MC miRNA is found in trophoblast-derived exosomes and can attenuate viral replication in cells through autophagy, thus acting as an antiviral mechanism to protect the fetus [59, 68, 69]. RIG-I-like receptors (RLR) can also recognize viral DNA, and have been implicated as being important to EBOV resistance via signaling of IFN antagonists such as VP35 and VP24 [70, 71].

4. CLINICAL PRESENTATIONS AND MATERNAL FETAL OUTCOMES

Case studies from previous epidemics report an 89–93% fatality rate amongst pregnant women and perinatal mortality at 100%, with no reports of neonates surviving transplacental EBOV for longer than 19 days [72–74]. Table 1 highlights four reported pregnancy related EBOV cases from 2012–2015 with more details provided in the actual case presentations. It is of interest to note that while maternal outcomes varied, all four cases resulted in fetal death [50, 61, 75].

In the first case listed in Table 1, pathological findings in the placenta included the presence of maternal macrophages found within the intervillous space, with degenerate appearing nuclei, cytoplasmic blebs, and eosinophilic cytoplasmic granules, suggestive of viral inclusions. In addition, immunohistochemical staining with EBOV antigen showed circulating, large atypical maternal mononuclear cells with the antigen also being present in foci in the villous syncytiotrophoblasts. No virions were detected with transmission electron microscopy, and no malarial parasite pigmentation or parasitized erythrocytes were seen [61].

To this day, it remains incompletely understood how pregnancy outcomes are affected in women who conceive after having recovered from EBOV. In 2016, data in Liberia was evaluated from 70 pregnant women who had conceived post recovery. Of these 70 women, 15 had miscarriages, and 4 neonates were born stillborn, with all 15 miscarriages occurring 4 months or longer post-discharge from an Ebola treatment center [21]. Overall, the fetal death rate is nearly 100% in pregnant women with EBOV, regardless of maternal outcomes [76].

In one female survivor of EBOV of child bearing age, there has also been a report of virus relapse in the central nervous system [78]. The data collected in these studies suggests that EBOV can threaten reproductive health even after the disease has been clinically resolved. In men, EBOV RNA can be shed in semen for at least 18 months after the disease onset [79].

To date, only one case of a newborn to survive congenitally acquired EBOV, as a result of experimental therapies, has been reported. Briefly, the neonate was delivered at 36 weeks' gestation by an EBOV positive mother, and also tested positive for EBOV herself. Permission was granted to treat the child with three experimental therapies: monoclonal antibodies (ZMapp), a buffy coat transfusion from an EBOV survivor, and also GS-5734 (Gilead Sciences) a broad spectrum anti-viral. In EBOV infected rhesus monkeys, there has been a demonstrated 100% survival rate when given GS-5734 for up to 3 days post-infection [80]. Acetaminophen was also given as a pre-medication. Though the infant suffered with episodes of myoclonic seizures, there were no pathological signs of liver or kidney damage, and neurological function were normal. The neonate is considered to have made a full clinical recovery, but further research is still needed in order to determine if the survival outcome can be attributed to one therapy, or a combination of all three [34]. Dörnemann *et al.* states that favorable outcomes in this case could also have been attributed to viral transmission having possibly occurred late in pregnancy, and also limited during the brief period of labor, having resulted in the neonate having a low viral load at birth. The mother

was also administered the anti-viral, Favipiravir, which could have also had an effect on EBOV replication in the fetus.

5. THE FUTURE OF EBOV IN PREGNANCY

The largest recorded outbreak of EBOV is now in the past, with a total of 28, 652 (suspected, probable, and confirmed) cases and over 11,000 reported deaths [81]. On March 29, 2016, the World Health Organization terminated the “Public Health Emergency of Public Concern” for the EBOV outbreak in West Africa, though 2 confirmed and 3 possible outbreaks have been confirmed since then [82].

In the event of another EBOV outbreak, and in order to fully understand the pathogenesis of EBOV in both the pregnant population and in neonates, it is imperative that the sampling of placental tissue becomes routine procedure in order to aid in the development of new methods of treatment and prevention. The automatic exclusion of pregnant women from clinical trials has denied EBOV infected mothers the ability to benefit afforded to others, as results from studies that do not include pregnant women cannot be extrapolated to pregnancy [31]. In addition, because so many pregnant women infected with EBOV had coinfections with malaria, further research needs to be done on the clinical outcomes and interactions associated with these two simultaneous infections [61]. The infectivity of the amniotic fluid in mothers in the convalescent phase also needs to be studied further.

As we continue to learn more about EBOV transmission during pregnancy, along with its clinical course of illness and the fate of neonates born EBOV positive, the health needs of mothers needs to be better understood as opposed to delaying obstetrical interventions in order to manage the risk of transmitting EBOV to healthcare workers. Ensuring that the proper procedures to strengthen healthcare systems are taking place, such as having better access to PPE during labor, along with standardized procedures to be used in Ebola treatment centers, will only help to avoid the inevitable adverse effects that EBOV has been shown to have on women’s reproductive health.

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Table 1.

Summary of Four Reported EBOV Pregnancy Related Cases: 2012–2015.

Case History	Maternal Test Results	Maternal and Fetal Outcomes
Age:29 (2012, DRC) Symptoms: Fever, abdominal pain, uterine contractions, vomiting, diarrhea, vaginal bleeding, fatigue Admitted: Day 4 of symptoms Months pregnant: 7 Fetal Movement: Normal Treatment: Rehydration, antibiotics, anti-malarial drugs.	EBOV Positive: RT-PCR, IgM ELISA Other Positive: Malaria	Maternal: Spontaneous vaginal delivery two days after admission with rapidly deteriorating health. Comatose and death followed two days after delivery. Fetal: Appeared healthy at birth. Blood collected was positive for EBOV one day after birth. Over several days, neonate became quiet, febrile and inactive. Seven days post-delivery, infant developed respiratory distress, followed by coma and death [77].
Age: 40 (2014, Guinea) Symptoms: Fever and abdominal pain (initially), followed by vaginal bleeding several weeks later Months pregnant: 4 Fetal heartrate: Within normal range Fetal movement: Daily Treatment: Recommended that patient remain near an Ebola treatment center until delivery.	EBOV Positive: RT-PCR (1st test) 5 Days post-admission: RT-PCR negative for EBOV and afebrile 38 Days post-admission: Amniotic fluid, placental swab and cord blood test positive for EBOV via RT-PCR	Maternal: Spontaneous delivery of stillborn fetus at 5 months. One week post-delivery, left Ebola treatment center in good condition. Fetal: Stillborn [50].
Age: 22 (2015, Sierra Leone) Symptoms: Anorexia, muscle pain, joint pain, fever Months pregnant: N/A Fetal heartrate: Within normal range Fetal movement: Daily Treatment: Upon patient request, discharged from Ebola treatment center 2 weeks after admission and negative RT-PCR for EBOV. Patient and her family were advised to self-isolate.	EBOV Positive: RT-PCR (1st and 2nd test) 6 Days post-admission: RT-PCR negative for EBOV 3 Weeks post-discharge, upon return to Ebola treatment center: Placenta (expelled) tested positive for EBOV, maternal blood tested negative for EBOV.	Maternal: After expelling placenta and fetus, patient was discharged in good health. Fetal: Intrauterine fetal death [50].
Age: 20 (2015, Sierra Leone) Symptoms: Fatigue, confusion, jaundice, eye pain, abdominal pain Months pregnant: 7 Treatment: Patient did not seek medical care until 21 day quarantine was over, as a result of her husband being positive for EBOV. When fetal movements and heartbeat were not detected, patient was given medication to induce labor.	EBOV Positive: IgM and IgG ELISA Other: Maternal RT-PCR EBOV negative, stillborn infant RT-PCR EBOV positive.	Maternal: Survived Fetal: Stillborn and deformed [75].