JOGECA 2018; 29(1): 17-24

Infection in pregnancy; understanding impact on placental microenvironment and preterm birth: a review

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Abstract

Background: Pregnancy increases susceptibility to and severity of infections caused by certain microbes and parasites. The presence of these infectious agents at the maternofetal interface may lead to adverse pregnancy outcomes including preterm birth either via direct action of the microbes or indirectly via alteration of the placental microenvironment.
Objective: To summarize the literature regarding the role of various infectious agents in alteration of placental microenvironment and predisposition to preterm birth.
Method: A review search using Google scholar, PubMed, Cochrane Library and Trip database was conducted at the University of California San Francisco. A total of 880 abstracts were reviewed and a total of 95 studies were included. Studies were included if they reported any information on infection during pregnancy, effect on placenta or fetal membranes or risk of preterm birth.
Results: The current evidence indicates that various infectious agents affect pregnancy and alter placental microenvironment at the maternofetal interface. Severity of these infections increases with gestation. Additionally, these infections are associated with the risk of adverse obstetric outcomes including preterm birth.
Conclusion: Prevention, early detection and treatment of these infections including those that are asymptomatic is important in maintaining integrity of the placenta and in reducing the burden of preterm births.

Key words: Infection, HIV, Zika, Malaria, Placenta, Preterm birth, Structure

Introduction

Pregnancy increases the severity of and susceptibility to infections from a number of microorganisms. This is partly due to modulation of the immune system with suppression of cell-mediated immunity in favour of humoral immunity (Th1-Th2 shift) and partly due to the general physiological changes in pregnancy (1,2). Infections that increase in severity during pregnancy include Group B streptococcus, bacterial vaginosis, urinary tract infections, measles, herpes simplex, Zika virus, Hepatitis E virus, influenza, and varicella. Those that pregnant women become susceptible to include; Malaria, listeria monocytogenes, and toxoplasmosis gondi. These infections demonstrate tropism to placenta and run a more severe course in pregnancy. Although Human Immunodeficiency Virus (HIV) has a well-known adverse profile on pregnancy, it is unclear whether pregnancy affects its natural course. Most infections during pregnancy are subclinical and are only identified during routine screening. In certain instances, infections have been associated with adverse pregnancy outcomes such as spontaneous abortion, stillbirth, low birth weight, preterm birth and deleterious sequelae in the surviving neonate.

Preterm birth (PTB) affects approximately 10-18% of all pregnancies worldwide and leads to early infant morbidity, mortality and chronic childhood diseases (3). Characteristically, it accounts for over one million deaths in children below five years of age especially in developing countries where access to neonatal and infant care services are scarce. Although its pathophysiology is not fully understood, multiple factors have been implicated to increase a woman's risk of PTB, they include, extreme maternal age, short inter-gestational period, chronic illnesses such as hypertension and diabetes, low maternal socioeconomic status, ascending intrauterine infections and attendant fetal inflammatory response (4–6). The mechanism by which infection contributes to preterm labor is not well understood. It has been suggested that infectious agents and their products attach to Toll-Like Receptors (TLRs) resulting in an increased expression of inflammatory chemokines (IL-8, CCL-2), cytokines (PAF, IFN-γ, TNF-α and IL-1β), proteases (MMP-8 and MMP-9), and prostaglandins (PGE2 and PGF2 alpha), promulgating an environment that triggers labour (5,7,8).

In pregnancy complications, the placental structure is altered (9–13). Placental alterations comprising

of chorioamnionitis, fibrin deposition, formation of syncytial knots, villitis, villous stromal fibrosis, infarction, deciduitis or decidual necrosis have been linked to pregnancies complicated by infections. The mechanistic pathway leading to preterm birth from these alterations remains poorly understood but could be attributed to the aforementioned inflammatory changes (14–18).

Due to serious maternal and fetal health complications arising from infection during pregnancy, a better understanding of placental microenvironment, a fetal shield from the contiguous maternal infection, is crucial to the development of preventive and therapeutic strategies.

Objective: This literature review aims to discuss the main scientific evidence regarding the association between infection, placental microenvironment and preterm birth.

Methods for review

A review search using Google scholar, PubMed, Cochrane Library and Trip database was conducted. A total of 880 abstracts were reviewed and a total of 95 studies were included. Studies were included if they reported information on any of these topics; infection during pregnancy, effect of infection on placenta or fetal membranes or risk of preterm birth or prematurity. From the selected articles, their reference lists were also examined to identify more articles that contained relevant material to the subject of our review.

Results

We extracted relevant material from 95 publications, synthesized and summarized per infectious agent we felt were more relevant to our subject. The current evidence indicates that various infectious agents affect pregnancy and alter placental microenvironment at the maternofetal interface. Severity of these infections increases with gestation. These infections pose a risk of preterm birth in addition to other adverse pregnancy outcomes.

Group B *Streptococcus*

Group B *Streptococcus* (GBS), also known as *Streptococcus agalactiae,* is a β-hemolytic gram-positive coccus. It can be found as part of the normal vaginal, rectal and oral microflora. The burden of GBS in developing countries is high and is associated with adverse pregnancy outcomes such as cystitis, chorioamnionitis, endometritis, preterm birth and stillbirth (4,19,20-24). In the worst case scenario, GBS may lead to maternal meningitis, bacterial endocarditis, and death.

GBS penetrate the placental membranes and transinfect the amniotic fluid and fetal organs via the hemolytic pigments released by the bacteria. Within the placental membranes and amniotic fluid, GBS elicits over production of neutrophil-recruiting cytokines and chemokines but the presence of the hemolytic pigments impairs proper phagocytic function of the neutrophils leading to formation of Neutrophil Extracellular Traps (NET) that further damage the placenta and worsen the severity of GBS infection in pregnancy (25-28).

Bacterial vaginosis

Bacterial Vaginosis (BV) is a common but complex clinical condition in which the normal hydrogen peroxide producing lactobacilli is replaced with an overgrowth of anaerobic bacteria. The spectrum of this bacteria include *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma, urealyticum, Mobiluncus* spp., *Prevotella* spp. and *Bacteroides spp* (29,30). BV is a strong independent risk factor for adverse pregnancy outcomes including preterm birth (21,31,32). The bacteria may ascend in the upper reproductive tract colonizing both the amniotic fluid and placental membranes and the basal plate resulting in villitis, deciduitis and chorioamnionitis (33–35).

Measles

Measles during pregnancy is a cause of recurrent abortions, premature labour, and increased risk of fetal/neonatal loss (36,37). The incidence, symptoms and signs of measles during pregnancy tend to be worse than in a non-pregnant state explained by the changes in physiological and immune functions (38,39). The placenta from measles infected mothers is characterized by extensive and global fibrin deposition extending from the subchorionic space to the decidual area, with infarcted villi. Intervillous space demonstrates scattered neutrophils and collections of karyorrhectic cells while some syncytiotrophoblast contain intranuclear and intracytoplasmic inclusion bodies (40,41). These findings suggest that placenta from patients with measles in pregnancy harbors salient features that may contribute to adverse obstetric outcomes including preterm labour and birth.

Herpes simplex virus

The seroprevalence of Herpes Simplex Virus (HSV) during pregnancy is 14%. Pregnancy increases the severity of HSV with a possible systemic dissemination and higher risk for herpes hepatitis (42,43). Genital herpes during pregnancy is associated with preterm birth, spontaneous abortion, congenital and neonatal herpes and the worst case scenario, both fetal and maternal fatalities (44). When a pregnant woman acquires HSV in late pregnancy, she does not develop antibodies necessary to suppress viral replication posing a greater risk of perinatal complications. Vertical transmission of HSV can occur via transplacental hematogenous route at the time of delivery or during breastfeeding (45,46).

Within the placenta, HSV infection is usually more focal in the decidua (47) but microscopic findings are non-remarkable for both the absence of inflammation and characteristic viral inclusions (48) although deciduitis and villitis in relation to HSV have been cited in other literature (49). In early pregnancy, HSV 1 penetrate extravillous trophoblast mediated by the presence of HveA, HveB, and HveC core receptors with impairment of placental attachment and invasion to the uterine wall, a frequent cause of early spontaneous abortion (50). In late gestation, villous STB do not express surface core receptors for HSV 1 and are therefore resistant to its penetration. This explains the lower risk of HSV vertical transmission.

Zika virus

Zika virus (ZIKV) infection, transmitted by Aedes mosquito, is associated with fetal anomalies, postnatal infection, and fetal demise with a relatively mild clinical course in the mothers. Pregnant women have prolonged viraemia with greater persistence of ZIKV in the circulation and the fetoplacental unit (51). The persistence of the virus within the fetoplacental unit predisposes to a possible self-reinfection. The inability of maternal immune system to clear ZIKV during pregnancy and persistence of this virus in the fetoplacental unit contributes to a wide spectrum of adverse pregnancy outcomes such as spontaneous abortions, Intrauterine Growth Restriction (IUGR), oligohydramnios, stillbirth and preterm delivery; and a wide range of congenital abnormalities associated with ZIKV infection *in utero* (52). The notable effect of the ZIKV infection in pregnancy is Congenital Zika Syndrome (CZS) characterized by; severe microcephaly, reduced cerebral cortex with subcortical calcification, macular and optic nerve damage, congenital contractures and hypertonia (53,54).

Placental changes associated with ZIKV infection include placental infarction, villous stromal calcifications, prominently enlarged, hydropic chorionic villi with hyperplasia, pathognomonic chronic decidualitis with plasma cell infiltration, and focal proliferation of Hofbauer cells. Curiously, there are no features of acute or chronic villitis, villous necrosis, chorioamnionitis, funisitis, or hemorrhages (55–57).

Influenza

Pregnancy poses a greater risk in women with influenza virus infection. These women suffer a more severe illness compared to a normal population attributable to damage to the already constrained volumes of the lungs. The resulting morbidity leads to spontaneous abortions, preterm birth and at worst maternal mortality (58–60). In early pregnancy, influenza may cause hyperthermia which may lead to neural tube defects, hydrocephalaus, congenital heart defects, cleft lip and limb reduction defects (61). In advanced pregnancies, influenza may lead to fetal tachycardia and febrile illness. In labour it may lead to an increased risk of neonatal seizures, newborn encephalopathy, cerebral palsy, and death (62).

The placenta of patients with influenza shows abundant histiocytes in the maternal space, increased incidence of fibrinoid necrosis at the decidua and the intervillous space (60).

Malaria

Malaria caused by malarial parasite is a serious disease of major public health concern in endemic countries. There are four parasites that can cause malaria; *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae*. In pregnancy the susceptibility and severity of malaria infection is greater than in non-pregnant state. In countries with high prevalence and stable transmission, most people have developed immunity against malaria including pregnant women and are therefore at a lower risk of symptomatic clinical malaria. Pregnant women, however, are unable to clear malaria parasites from their system (63–66). In unstable transmission, pregnant women have a lower acquired immunity and malaria infections are likely to be symptomatic with a clinical disease running a full course (67). The disease is associated with adverse obstetric outcomes such as anaemia, stillbirth, spontaneous abortion, preterm birth, and both maternal and fetal demise. The risk seems to increase with gestational age and is inversely related to parity (68–70).

Infected erythrocytes in pregnancy, express *Plasmodium falciparum* erythrocyte membrane protein 1, 2 and 3 (Pf EMP 1, 2 and 3) encoded by VAR2CSA gene, histidine-rich protein I and II, sequestrin, rosettins and ring-infected erythrocyte membrane surface antigen (Pf 155/RESA) receptors, collectively termed as variant surface antigen-pregnancy associated malaria (VSAPAM). These receptors can bind intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), chondroitin sulfate A (CSA), CD36, TSP, and endothelial leukocyte adhesion molecule-1 (ELAM-1)(71,72). *Plasmodium falciparum* infected erythrocytes in pregnancy preferentially bind CSA resulting in sequestration of these erythrocytes and immune complexes in the intervillous spaces of placenta; a hallmark of pathology of malaria in pregnancy. As a result of deposition of Red Blood Cells (RBCs), malarial pigments, the placenta turns black. In addition, the infected placenta demonstrates perivillous fibrinoid deposits, Tenney-Parker changes and this may impair mother to fetus transfer (73,74). These pathological findings have a bearing on impaired apoptosis and increased oxidative stress in the placenta of malaria infected women (75).

Listeria monocytogenes

Listeria monocytogenes is a cause of listeriosis, a foodborne illness. This bacteria is a small, facultative anaerobe, Gram-positive, flagellated, linear motile rod, which is non-spore forming. Pregnant women are 20 times at greater risk of the disease than the general population. Listeriosis presents with mild, flu-like symptoms such as fever, chills, muscle aches, and diarrhoea or stomach upset. The infection may easily pass unnoticed in many pregnant women but has serious consequences on the fetus including the risk of stillbirth, spontaneous abortion and prematurity (76–78).

Listeria monocytogenes induced placental changes include acute necrotizing chorioamnionitis with funisitis, a green-yellowish discoloration and thickening of the chorioamniotic membranes, vasculitis, thrombosis, dense and diffuse inflammatory neutrophilic exudates, often forming subchorionic abscesses and necrosis of the decidual spiral arteries and the presence of intracellular gram-positive bacteria in membranes, umbilical cord and intervillous maternal circulation and villous capillaries. *Listeria monocytogenes* seems to have tropism for gravid uterus and target the extra villous trophoblast that penetrate into the decidua and maternal spiral arteries (79–81).

Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is a tiny retrovirus belonging to the genus lentivirus. On its surface is a glycoprotein 120 (gp120), which it uses to bind to and infect a range of CD4+ leukocytes. It demonstrates high mutation rates both within and between individuals. Pregnancy does not aggravate the natural history of HIV infection in women although adverse pregnancy outcomes have been reported in HIV positive women on treatment. They include; increased rates of spontaneous early abortion, intrauterine growth restriction, stillbirths, preterm birth, and other infectious complications (82,83). Our previous work and other data suggest that HIV/ART is associated with placental changes that may predispose to preterm birth. These changes include; chorioamnionitis, massive perivillous fibrin deposition, thrombosis and infarction, formation of syncytial knots, and syncytiotrophoblast sloughing, villitis, villous stromal fibrosis, abnormal villous maturation, deciduitis or decidual necrosis and neoangiogenesis (15,18,84).

Neglected tropical infections in pregnancy

A number of neglected tropical infections affect women in reproductive age. Little attention has been given to such infections although they affect over 1 billion people living within the tropics and subtropics. The common ones include schistosomiasis, leishmaniasis and other helminthic infections.

Although schistosomiasis belongs to a broader class of helminthic infections, it deserves a special mention due to a large number of people affected by this worm. Schistosomiasis is a parasitic infection that affects about 200 million people. There are three species of schistosome infecting humans: *Schistosoma japonicum, Schistosoma mansoni* and *Schistosoma haematobium.* The worms mainly affect the gut, hepatosplenic and urinary systems causing chronic inflammation (85). *Schistosoma haematobium* affects the female genital structures via direct entrance of the eggs from the adjacent urinary system to the uterus, fallopian tubes and ovaries (86). In pregnancy, schistosomiasis can result into severe anaemia, intrauterine growth restriction and other adverse pregnancy outcomes (87). Schistosomiasis can infect the placenta causing global inflammation, involving proinflammatory cytokines, and the worm may pass to the fetus resulting in congenital schistosomial infection (88).

Leishmaniasisis caused by the *protozoan leishmania* parasites which are transmitted by the bite of infected female phlebotomine sandflies. There are three forms of this disease; visceral (kala-azar), cutaneous and mucocutaneous. Leishmaniasis infection with the Viscero Tropic (VL) form is the most serious form and has been described during pregnancy, resulting in vertical transmission and fetal loss when treatment failure occurs. Kala-azar caused by *Leishmania chagasi* is characterized by persisting fever, weight loss, asthenia, adynamia and anaemia. The disease is fatal when untreated, and could result in death within 2 years after the onset of clinical symptoms and signs. Although there is limited data on transplacental vertical transmission of VL, some observational studies have confirmed this possibility (89,90).

Finally, other helminthic infections caused by nematodes, filarial worms, platyhelminthes, cestodes and trematodes have been described in pregnancy. They are widespread infectious agents of human populations affecting mainly poor populations in sub-Saharan Africa, Asia and parts of America (91,92). Data confirming susceptibility of pregnant women to these infections is conflicting. When present during pregnancy, these infections affect both the mother and fetus. Helminths use similar mechanisms of immune tolerance like the human fetus in the host to avoid maternal immune responses by modulating Th1 and Th2 responses and affecting the T cell regulatory responses. The adverse pregnancy outcomes caused by these infections include, severe maternal anaemia, malnutrition, prematurity and pregnancy wastage (93–95). Their effect on placenta has been described under schistosomiasis.

Given these observations, it is plausible to state that various infections in pregnancy lead to features of placental inflammation with production of proinflammatory cytokines. These cytokines may in turn activate maternal immune system aggravating

further damage to the placental structure and initiating preterm labour.

Conclusion

The current evidence indicates that various infectious agents affect pregnancy and alter placental microenvironment at the maternofetal interface. Severity of these infections increases with gestation. Additionally, these infections are associated with the risk of adverse obstetric outcomes including preterm birth. Prevention, early detection and treatment of these infections including those that are asymptomatic is important in maintaining integrity of the placenta and in reducing the burden of preterm births.

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