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## Influence of Infection During Pregnancy on Fetal Development

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### Abstract

Infection by bacteria, viruses and parasites may lead to fetal death, organ injury or limited sequelae depending on the pathogen. Here we consider the role of infection during pregnancy on fetal development including placental development and function, which can lead to fetal growth restriction. The classic group of teratogenic pathogens are referred to as “TORCH” (*Toxoplasma gondii*, Others like *Treponema pallidum*, Rubella virus, Cytomegalovirus, Herpes simplex virus), but should include a much broader group of pathogens including Parvovirus B19, *Varicella zoster* virus, and *Plasmodium falciparum* to name a few. In this review, we describe the influence of different infections *in utero* on fetal development and the short- and long-term outcomes for the neonate. In some cases, the mechanisms used by these pathogens to disrupt fetal development are well known. Bacterial infection of the developing fetal lungs and brain begins with inflammatory cascade resulting in cytokine injury and oxidative stress. For some pathogens like *P. falciparum*, the mechanisms involve oxidative stress and apoptosis to disrupt placental and fetal growth. An *in utero* infection may also impact the long-term health of the infant; in many cases, a viral infection *in utero* increases the risk of developing Type 1 diabetes in childhood. Understanding the varied mechanisms employed by these pathogens may enable therapies to attenuate changes in fetal development, decrease preterm birth, and improve survival.

### Introduction

Despite eradication of smallpox and near elimination of polio, the world continues to harbor a variety of pathogens that can cause significant damage to the fetus *in utero*. In this review, we discuss the bacteria, viruses and parasites associated with fetal death, organ injury or other effects on fetal development. The greatest burden of disease remains in low and middle-income countries. For example, cases of congenital rubella syndrome (CRS) are vastly underreported, but it was estimated recently that CRS affected 46,000 infants annually in the Southeast Asia alone. Exposure to malaria *in utero* contributes to 100,000 childhood deaths as a result of severe fetal growth restriction. Finally, one of the most

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endemic pathogens in South America is the parasite *Trypanosoma cruzi*, which causes Chagas disease. *T. cruzi* infects about 30% of the population in Latin America (10,000,000 people) and more than 15,000 infants in Latin America annually. Mechanisms of injury, in particular inflammatory pathways from bacterial infection impacting the fetal lung and brain, are considered in detail. Finally, we focus on knowledge gaps and future research directions to minimize the worldwide morbidity and mortality from fetal infections.

### **Intrauterine bacterial infection and fetal outcomes (1,300 words, 25 refs)**

The majority of early preterm births are associated with intrauterine infection, which triggers an inflammatory response believed to result in preterm labor (PTL) and injury to the developing fetal lung and brain.<sup>3-5</sup> Chorioamnionitis is the histologic term to describe a neutrophilic infiltration of the fetal membranes (chorioamnion), generally associated with a bacterial placental infection. Severe chorioamnionitis may also be associated with neutrophil invasion of the umbilical cord, called funisitis. Infection-associated preterm birth has been hypothesized to result from bacterial trafficking from the lower genital tract into the uterus. Whether bacteria traffic from the vagina into the uterus routinely during pregnancy or only under special conditions is unknown. Interestingly, carbon particles traffic from the vagina into the abdominal cavity within 30 minutes in non-pregnant women suggesting that rapid organ-to-organ migration routes exist.<sup>1</sup> Bacteria recovered from the amniotic fluid and fetal membranes generally consist of organisms that colonize the vagina including gram-negative (e.g. *Escherichia coli*, *Gardnerella vaginalis*), gram-positive (*Group B Streptococcus*), and anaerobic (*Mycoplasma hominis*) bacteria (Fig. 1).<sup>4, 6, 7</sup> No single lower genital tract bacteria studied by these investigators was associated with a higher risk for preterm birth with the possible exception of *Trichomonas vaginalis*, which increases the risk of preterm premature rupture of the membranes.<sup>2</sup> Recently, pathogenic vaginal flora associated with bacterial vaginosis was discovered to contain newly recognized bacterial species previously unknown because they were unable to be cultivated using standard techniques.<sup>3</sup> These fastidious (non-cultivable) bacteria include *Leptotrichia/Sneathia*, which has also been associated with preterm birth.<sup>4-6</sup>

The inflammatory cascade remains a central mechanism of preterm birth and fetal injury triggered by bacterial infections. Pro-inflammatory cytokines and chemokines, small immunologic proteins, likely play a central role in the pathogenesis of infection-associated preterm birth and fetal injury.<sup>9</sup> Bacterial products stimulate the production of cytokines from many different placental tissues including chorioamnion, decidua and trophoblast cells.<sup>7-9</sup> Cytokines most frequently measured in studies of preterm birth are interleukin-1 beta (IL-1 $\beta$ ), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor (TNF- $\alpha$ ), CXCL8, and CXCL10. IL-1 $\beta$  and TNF- $\alpha$  are considered central to the pathway, because amniotic fluid infusion of either cytokine in a nonhuman primate model is capable of inducing preterm birth.<sup>10</sup> Cytokines stimulate prostaglandin production in other placental tissues (amniotic epithelial cells and decidua), which further drive labor.<sup>14, 17, 18</sup>

Two bacterial infections, *Listeria monocytogenes* and *Treponema pallidum*, are worth special mention, because their fetal sequelae are typically more severe. *Listeria monocytogenes* is a Gram-positive rod associated with ingestion of raw meats, unwashed

raw vegetables and soft unpasteurized cheeses; fetal sequelae are severe with spontaneous abortion in 10–20%, intrauterine fetal death in 11%, and preterm birth in 50%.<sup>11</sup> *L. monocytogenes* may spread to the uterus via either an ascending infection or a hematogenous route. Extravillous trophoblasts efficiently control the spread of *L. monocytogenes* at the maternal-fetal interface by confining the bacteria within vacuolar compartments destined for lysosome degradation; however the placenta continuously reseeds maternal organs with bacteria until the placenta is expelled after delivery.<sup>12,13</sup> The mechanism of fetal death may result from impaired suppression of maternal T cells to fetal antigens by maternal Foxp3+ T regulatory cells.<sup>14</sup> *Treponema pallidum* (syphilis) is a spirochete bacterium that if untreated will lead to early fetal loss, preterm birth, stillbirth, low birth weight, and congenital disease in more than half of women with active disease.<sup>15</sup> Fetal manifestations involving multiple organs may be divided into early congenital syphilis (first 2 years of life) and late congenital syphilis (first 2 decades, Table 1).

### Infection-associated injuries to the fetal lung

Intra-amniotic infection and inflammation is associated with fetal lung injury, aberrant lung development and the resulting neonatal and adult chronic lung disease.<sup>16,17</sup> The extent of fetal lung injury is likely influenced by the the type, timing, and duration of the infection/inflammatory response. Intrauterine infections has been associated with an increased incidence of bronchopulmonary dysplasia (BPD) and a reduction in respiratory distress syndrome (RDS). In some studies, a lower incidence of RDS in infants exposed to chorioamnionitis has led to the hypothesis that *in utero* inflammation stimulates interleukin-1 $\alpha$  production, which acutely increases synthesis of surfactant and lipid proteins in the fetal lung thus lowering RDS.<sup>18</sup> Inflammation also disrupts fetal lung development by altering the biological program necessary for lung morphogenesis and vasculogenesis, which closely mimics the histology seen in BPD. BPD is a multi-factorial chronic lung disease of preterm infants, that affects 35% of infants weighing less than 1,500 grams.<sup>19</sup> Arrested alveolar development, a hallmark of BPD, may have long-lasting detrimental effects on ultimate lung development.<sup>20</sup> Many former preterm infants also develop significant pulmonary disease as adults, which can manifest as chronic obstructive pulmonary disease or as asthma.<sup>21–28</sup>

BPD is characterized by disrupted alveolar development, large airways with inflammation, interstitial fibrosis, and impaired pulmonary angiogenesis.<sup>29,30</sup> Since clinically apparent BPD is not always present in preterm infants born after chronic chorioamnionitis, other postnatal pro-inflammatory factors likely also play a role including exposure to mechanical ventilation, hyperoxia, and sepsis.<sup>17,31</sup> Studies have linked elevated cytokines in the amniotic fluid with an increase in BPD and neonatal morbidity/mortality.<sup>16,32,33</sup> In a large prospective cohort study involving 1067 preterm infants (606 infants developed BPD), increased serum IL-8 and IL-10 and decreased levels of RANTES (regulated on activation normal T cell expressed and secreted) protein at less than three days of age were associated with an increased risk for developing BPD.<sup>34</sup> However, with the use of antenatal steroids, the association of intrauterine infection and BPD is now less clear. A recent meta-analysis (15,295 patients, 59 studies) demonstrated only a modest association between chorioamnionitis and BPD (OR 1.58, 95% CI 1.11 to 2.24).<sup>35</sup> While the definitive role of

intrauterine infection and inflammation on fetal lung and subsequent BPD development remains unclear, substantial evidence exists associating intrauterine infection/inflammation with fetal lung injury.

The mechanisms underlying alveolar arrest associated with intrauterine inflammation have recently begun to be elucidated in animal models. The injurious effects of intrauterine infection/inflammation on the fetal lung have been demonstrated in sheep using an intra-amniotic injection of lipopolysaccharide (toxic component of gram-negative cell walls), which led to increased amniotic fluid IL-1 $\beta$ , IL-6 and IL-8 mRNA expression; fetal lung inflammation was characterized by increased neutrophils and pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8 and monocyte chemoattractant protein).<sup>36-38</sup> Recently, a nonhuman primate model provided a more comprehensive description of the inflammatory pathways induced by amniotic fluid cytokines and the impact of fetal lung angiogenesis and morphogenesis.<sup>39</sup> Following a limited choriodecidual infection with Group B Streptococcus, a pro-inflammatory cytokine response ensues, leading to elevated amniotic fluid cytokine levels (TNF- $\alpha$ , IL-8, IL-1 $\beta$ , IL-6). Normal fetal swallowing of amniotic fluid likely results in direct fetal lung exposure to pro-inflammatory cytokines triggering a pulmonary innate immune response with recruitment of neutrophils and macrophages. Four days later, fetal lung expression was significantly altered with increased gene expression associated with innate and adaptive immune responses and decreased gene expression associated with normal lung development (angiogenesis, morphogenesis, cellular development). A conceptual model depicting results from this study shows how an early Group B Streptococcal infection of the placenta can induce fetal lung injury (Figure 2).

Neonatal lung injury that begins *in utero* may also manifest as RDS, which is characterized by a lack of surfactant and collapse of distal airways. Histologic chorioamnionitis is typically associated with a decreased incidence of RDS, possibly as a result of intrauterine cytokines triggering maturation of the surfactant system.<sup>40,41</sup> However in very immature preterm infants with structural lung immaturity and more pronounced exposure to chorioamnionitis, lung injury may lead to severe clinical RDS postnatally.<sup>42</sup>

### **Infection-associated injuries to the fetal brain and other organs**

A fetal infection may result in a systemic inflammatory response that can persist postnatally, compounding injury to multiple organs; infants born to mothers with severe chorioamnionitis have elevated umbilical serum pro-inflammatory cytokines, including TNF- $\alpha$ , IL-6, IL-8 and IL-1 $\beta$ .<sup>43</sup> Chorioamnionitis has been associated with an increased incidence of injuries in preterm infants including the brain<sup>44,45</sup> (periventricular leukomalacia, PVL, intraventricular hemorrhage, IVH; cerebral palsy, CP), bowel<sup>46</sup> (necrotizing enterocolitis, NEC), and eye<sup>47</sup> (retinopathy of prematurity, ROP). Discrepancies in disease definition, patient populations, and study designs have led to difficulties in interpretation of the relationship between chorioamnionitis and some fetal conditions.

Although both clinical and histological chorioamnionitis has been associated with PVL<sup>48</sup>, a lack of an association with histological chorioamnionitis has also been reported.<sup>49</sup> Recently, mild intrauterine inflammation that was not sufficient to induce labor was correlated with

fetal and neonatal brain injury in a mouse model.<sup>50</sup> Intrauterine inflammation has also been associated with the long-term neurodevelopment disorders such as CP, the most common cause of severe physical disability in childhood.<sup>21,36</sup> A secondary data analysis from the Alabama Preterm Birth Study demonstrated that among children born between 23 and 32 weeks' gestation *in utero* exposure to acute inflammation was not associated with increased risk of severe adverse neurodevelopmental outcomes at age 6 years.<sup>51</sup> While intrauterine infection/inflammation appears to increase the risk for developing CP, incongruities in reported study results elucidate the complexity of understanding the underlying mechanisms between intrauterine infection/inflammation and brain injury that cause adverse long-term neurodevelopmental outcomes.

Intrauterine infection and inflammation may contribute to fetal brain damage by direct cellular injury or by enhancing cellular injury additively with other intra- and extra-uterine insults, such as hypoxia. Cytokines and inflammatory cells are thought to regulate many common pathways associated with perinatal brain injury including infection, toxin-mediated injury, hypoxic-ischemic injury, and reperfusion injury.<sup>45</sup> The presence of elevated amniotic fluid IL-1 $\beta$  and IL-6 is associated with white matter injury in infants.<sup>52</sup> TNF- $\alpha$  may play a key role in the induction of microglial-dependent toxicity in the presence of astrocytes.<sup>53</sup> A conceptual model for how a bacterial infection and cytokine production may induce perinatal brain injury is shown in Figure 3. Cytokines produced by the fetal membranes permeate the amniotic fluid where they are in direct contact with the fetal lung (via aspiration of amniotic fluid) or alternatively, may enter the fetus through hematogenous spread. Circulating fetal cytokines may then alter permeability of the blood-brain barrier allowing CNS access to bacteria, which can further propagate injury.

Fetal white matter oligodendrocyte progenitor cells (pre-oligodendrocytes) are particularly vulnerable to injury from activated microglia (brain macrophages), excitotoxicity and free radical attack.<sup>54,55</sup> Once injured, the pre-oligodendrocytes fail to differentiate into myelin-forming oligodendrocytes, which increase the risk for neurodevelopmental abnormalities like CP.<sup>56</sup> In extremely premature infants, placental inflammation and white matter injury diagnosed by cranial ultrasound was associated with development of diparetic cerebral palsy (diagnosed at 2 years post-term equivalent).<sup>57</sup> In studies of brain pathology, noncystic PVL is a risk factor for CP and was associated with reactive microglial accumulations at periventricular crossroads of growing axonal pathways within white matter.<sup>58</sup> Animal models also demonstrate an association between intrauterine inflammation, fetal microglial activation and subsequent motor deficits and behavioral abnormalities.<sup>55,59</sup> Interestingly, animal studies have also implicated perinatal hypoxia and inflammation in the microglia activation and white matter injury involved in neurodevelopmental disorders such as schizophrenia.<sup>60</sup>

## Viral Infection in Pregnancy and Fetal Outcomes

The prevalence of viral infection during pregnancy has been hypothesized to contribute to some cases of intra-amniotic inflammation associated with preterm birth. Several studies using quantitative real-time polymerase chain reaction (PCR) to test amniotic fluid in the second trimester have determined that between 2.2 and 8.4% of low-risk women with

normal fetuses on ultrasound have detectable genome sequences from at least one of eight viruses: adenoviruses, herpes simplex virus (HSV), varicella zoster virus (VZV), human herpesvirus 6 (HHV6), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), parvovirus B19, and enteroviruses.<sup>61</sup> HHV6 was the most common virus detected in amniotic fluid at 1.0%. Viral invasion of the amniotic cavity was not associated with a significant change the amniotic fluid white blood cell count, glucose or IL-6 level; however, C-X-C motif chemokine 10 (CXCL10) correlated with HCMV viral load. Fetal involvement appears rare with *in utero* infection by these viruses. Exploring mechanisms of disease for the viruses with the greatest potential to cause fetal morbidity and mortality requires further discussion of rubella virus, HCMV, and VZV. A focus on the human immunodeficiency virus (HIV) is also appropriate based on its global impact.

### Rubella virus

The devastating teratogenic effects of the rubella virus were first reported in 1941 by Dr. Norman Gregg, who recognized congenital cataracts and other deformities following rubella (German measles) infection in the mother during pregnancy.<sup>62</sup> The first and early second trimesters appear to be the most vulnerable periods in pregnancy for developing CRS secondary to a maternal infection. CRS occurs in nearly all fetuses affected before 8 weeks and there are few defects if maternal rubella is acquired after 17 weeks.<sup>63</sup> Manifestations of CRS are numerous (Table 1) with deafness being most common. Pathologic analysis of tissues from aborted fetuses infected with rubella reveal widespread non-inflammatory necrotic damage of the eyes (lens, iris, retina), heart (myocardium, endothelial cells in cardiac vessels), brain (vascular necrotic lesions in cerebral blood vessels) and ears (epithelium of cochlear duct).<sup>64</sup> The teratogenicity of rubella is likely due to several mechanisms including a direct cytopathic effect of the virus, which may trigger apoptosis, and inhibition of mitosis through cytoskeletal derangements resulting in a partial arrest of organ development.<sup>65</sup> A teratogenic mechanism that may be shared between rubella and HCMV is the interaction of viral products with the host retinoblastoma (Rb) gene, which regulates fetal cell growth.<sup>65</sup> In the case of rubella virus, the binding of the putative replicase (NSP90; critical for virus replication) to the Rb protein *in vivo* facilitates rubella virus replication, yet alters the normal function of Rb in cellular growth leading to teratogenesis. HCMV produces an immediate-early gene product (IE2 86), which interacts with Rb and has been hypothesized to partially explain the teratogenicity of HCMV.<sup>66</sup>

The observation of an increased risk of Type 1 diabetes following a congenital rubella infection prompted further study of the risk of neonatal or childhood viral infections on acquisition of Type 1 diabetes.<sup>67</sup> Epidemiologic studies have also associated other perinatal viral infections with an increased risk of acquiring Type I diabetes; these viruses include enteroviruses, coxsackie B viruses, HCMV, or mumps virus.<sup>68</sup> Type 1 diabetes is thought to occur as the result of molecular mimicry between viral pathogens (e.g. HCMV peptides) and pancreatic islet beta cell proteins in these cases. According to this theory, neonatal T cells reactive to viral peptides become cross-reactive to an antigen in the insulin-producing pancreatic beta islet cells resulting in an autoimmune destruction of the islet cells and Type 1 diabetes. Evidence for this theory remains controversial and difficult to study given the inaccessibility of the pancreas and long latency between viral infections and disease onset.

## HCMV

HCMV is perhaps the most common cause of congenital infections and is a leading cause of sensorineural hearing loss, brain damage and cerebral palsy in the United States.<sup>69</sup> Most congenital infections are asymptomatic and, therefore, disease prevalence is difficult to quantify. Children are common vectors for HCMV and pregnant women who are exposed to children in day-care centers or preschools are at higher risk for infection. Despite preconceptional immunity to HCMV, infection during pregnancy with new strains can result in fetal infection and congenital HCMV disease.<sup>70</sup> Like rubella, the risk of congenital HCMV disease is greatest with infection during the period of fetal organogenesis in the first and early second trimester. Interestingly, the risk for *in utero* transmission of HCMV is highest in the third trimester, but fetuses infected at this time are generally born healthy.<sup>71</sup> Amniotic fluid from pregnancies complicated by congenital HCMV infection had higher levels of multiple cytokines and growth factors than uninfected controls including TNF- $\alpha$ , IL-1 $\beta$ , IL-12, IL-17, CCL2, CCL4, CXCL10, granulocyte-macrophage colony-stimulating factor and platelet-derived growth factor BB.<sup>72</sup> Overall, the immune profile was associated with a shift toward the pro-inflammatory T helper type 1 (Th1) profile and away from the normal anti-inflammatory Th2 pattern of pregnancy. Induction of placental pro-inflammatory cytokines by HCMV in combination with a direct cytopathic effect may impair critical functions in the developing placenta and fetus: 1) syncytiotrophoblast cells may be more vulnerable to apoptosis, 2) placental vascularization may be arrested, and 3) cytokine diffusion into the fetus can directly impair development of the fetal brain.<sup>73</sup> These actions may lead directly to fetal growth restriction, preeclampsia, spontaneous abortion, stillbirth or preterm birth, which are features of congenital HCMV disease.

## Varicella zoster

The incidence of congenital varicella syndrome is unknown, but varicella is thought to infect 80 to 90 million people worldwide. Congenital varicella syndrome occurs most frequently when maternal disease is acquired between 8–20 weeks gestation. However, a maternal infection beginning within 5 days of delivery is associated with development of neonatal varicella with a 30% mortality rate; the high death rate likely reflects inadequate passive immunity received from the mother in the short time period before birth. Congenital varicella syndrome is very rare when maternal infection is acquired in the third trimester.<sup>74</sup> The widespread fetal damage that is typical of congenital varicella syndrome reflects both a hematogenous spread and its neurotropism (Table 1). A mechanism for fetal injury in congenital varicella syndrome was hypothesized based on the viral life cycle and the dermatomal pattern of skin lesions and segmental defects in the musculoskeletal system and autonomic nervous system. After a primary varicella infection, the virus becomes dormant within the sensory root ganglia unless reactivation occurs. Upon reactivation, the virus migrates down sensory nerves to the skin and causes a painful dermatomal rash referred to as herpes zoster. In the case of congenital varicella syndrome, viral “reactivation” in the spinal cord and ganglia is thought to occur after a very short primary infection phase.<sup>75</sup> Congenital varicella syndrome is thus considered to be similar to a herpes zoster *in utero*. Viral inflammation in the sensory root ganglia is thought to be responsible for the segmental

defects or anomalies of the skin, peripheral nervous, autonomic nervous and musculoskeletal systems, which all receive common innervations from the same spinal cord level.

## HIV

Currently, more than 33 million people live with HIV, which has had a disproportionate impact on the health of people in sub-Saharan Africa. Without therapy, approximately 15–30% of infants become infected during pregnancy with an additional 5–20% infected through breastfeeding.<sup>76</sup> Interventions to prevent mother-to-child transmission are well known, but a lack of resources and infrastructure continues to frustrate implementation of these interventions in many resource-poor countries. Studies have also documented a relationship between HIV seropositivity and increased risk of spontaneous abortion, stillbirth, intrauterine growth retardation, low birthweight and preterm birth<sup>77–82</sup> and neurodevelopmental delay.<sup>83</sup> The association between preterm birth and low birth weight has further been linked to the use of highly active antiretroviral therapy (HAART)<sup>84–86</sup>, maternal viral load<sup>87</sup> and maternal nutritional status<sup>88</sup> in HIV-seropositive women. HIV is also associated with an increase in chorioamnionitis and deciduitis, which may in part explain the elevated risk for preterm birth.<sup>89,90</sup> Interestingly, primary trophoblasts appear resistant to HIV infection, but *in vivo* trophoblast cultures support infection suggesting that leukocytes within the villous parenchyma (or membranes) may allow HIV-1 replication.

## Parasitemia in Pregnancy and Fetal Outcomes

Several parasites are known for vertical transmission and impairment of fetal growth and development (Fig. 1). Malaria in pregnancy is associated with fetal growth restriction, low birth weight, spontaneous abortion and intrauterine fetal death. *Toxoplasma gondii* is a highly prevalent infection throughout the world with human transmission generally occurring after ingestion of raw meat or exposure to cat feces; fetal damage is characterized by brain and eye injury. *Trypanosoma cruzi*, also known as Chagas disease, is endemic in Mexico, Central and South America. Congenital *T. cruzi* infection is associated with low birth weight, hepatosplenomegaly, anasarca, and stillbirth.

### **Plasmodium falciparum (Malaria)**

The most well defined parasitic mechanisms of fetal injury are described in malaria with *Plasmodium falciparum* being the most virulent of the Plasmodium species in pregnancy. More than 125 million pregnant women are at risk of malaria infection each year and at least 100,000 infant deaths can be attributed to malaria annually.<sup>91</sup> *P. falciparum* infects red blood cells (erythrocytes), which then circulate in the blood for about 18 hours. Subsequently, the parasite inserts adhesion molecules into the erythrocyte membrane to allow the infected erythrocyte (IE) to attach to host endothelium and sequester within an organ; by varying gene expression of these parasitic-encoded adhesion molecule, the IEs may alternatively bind ICAM-1, VCAM-1, CD36, or chondroitin sulfate A (or others) – all of which, are richly expressed by the placenta.<sup>92</sup> *P. falciparum* infection is associated with a massive IE sequestration to the syncytiotrophoblast surface (fetal trophoblast layer in contact with the maternal blood) in a first pregnancy. Whether the main effect of this sequestration is impaired blood flow to the fetus from capillary blockage (hypoxia) or



abnormal trophoblast invasion leading to poor placental vascularization (or both) is not known.

There is evidence for multiple mechanisms contributing to fetal growth restriction associated with malaria in pregnancy including impaired placental vascularization, production of growth hormones, placental amino acid transport, and altered immunologic milieu.<sup>91</sup> Recently, elevated complement C5a levels were correlated with critical factors enabling normal placental vascularization [angiopoietin-1 and -2, soluble endoglin and vascular endothelial growth factor receptor 1 (VEGFR1)] in a case-control study of 492 pregnant women in Malawi.<sup>93</sup> Genetic or pharmacologic inhibition of C5a or its receptor in a mouse model was associated with greater placental vascularization, fetal growth and survival. Together, this data suggested that elevations in C5a are a major driver of placental insufficiency and fetal growth restriction in pregnancies complicated by malaria. Fetal growth restriction in this setting has also been associated with decreased activity of system A, a key placental amino acid transporter. Another important mechanism centers on the shift in immunologic cytokine profile of sequestered placental cells from a typical immune profile associated with pregnancy, Th2, to an immune profile more suited to parasite killing (Th1). Finally, there is little evidence for a placental hypoxia model as a main cause of fetal growth restriction; however, whether fetal hypoxia might occur and limit growth is unknown.

### **Plasmodium vivax (Malaria)**

In addition to *P. falciparum*, *P. vivax* is the only other known Plasmodium species associated with malaria in pregnancy.<sup>94</sup> Similar to *P. falciparum*, *P. vivax* infection is more common in primigravid than multigravid women.<sup>95</sup> Malaria in pregnancy secondary to *P. vivax* can cause maternal anemia, fetal growth restriction, and miscarriage.<sup>66,96,97</sup> Infant's born to mothers infected by *P. vivax* are at risk for having a low birthweight (independent of anemia) and congenital malaria.<sup>94,98</sup> Maternal infection in the week before delivery has been associated with an increased risk for infant death from 1 to 3 months of age.<sup>99</sup> A Brazilian study demonstrated that compared to non-exposed women, placentas from *P. vivax* exposed women had increased syncytial knotting, thickness of the placental barrier and mononuclear cells.<sup>100</sup> Interestingly, unlike *P. falciparum* placentas, *P. vivax* placentas were without much evidence of placental parasites or hemozoin (malarial pigment) suggesting that *P. vivax* may have a decreased occupancy time in the placenta compared to *P. falciparum*. The mechanisms underlying the placental and fetal pathogenesis of *P. vivax* infection remain unclear.

### **Summary**

Teratogenic pathogens have classically been considered under the "TORCH" paradigm, but actually represent a much broader group of bacteria, viruses and parasites that can injure the fetus or impact placental development and function. In the developed world, intrauterine bacterial infections contribute significantly to early preterm birth. Extremely premature infants surviving after a bacterial intrauterine infection often sustain severe morbidity and long-term sequelae such as chronic lung disease, asthma, CP, and neurodevelopmental problems. Other pathogens are more important in specific geographic regions. For example,

acquisition of *P. falciparum* by the mother during pregnancy is a significant risk factor for preterm birth and neonatal death in Africa and Southeast Asia. Multiple factors may influence the extent of fetal injury associated with an inflammatory response including the triggering pathogen or cytokine profile, timing of the exposure, duration of the insult, concurrent insults (e.g., hypoxia, ischemia), infant demographic variables (e.g., ethnicity, sex), maternal factors (e.g., antenatal steroids, tobacco use), and genetic or epigenetic determinants. When designing research studies related to perinatal infection, consideration of these factors is needed to improve our understanding of mechanisms associated with fetal injury and to design prevention strategies.

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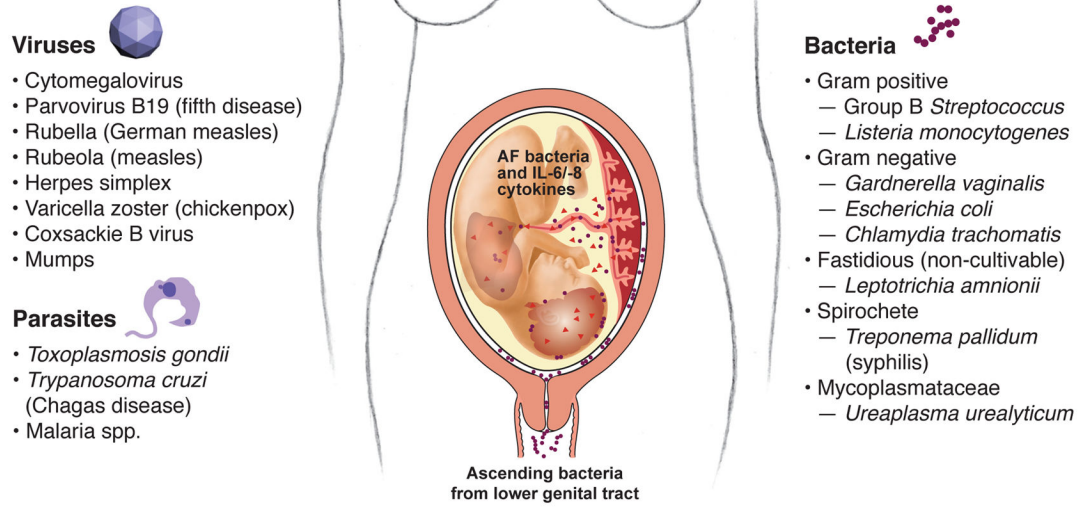
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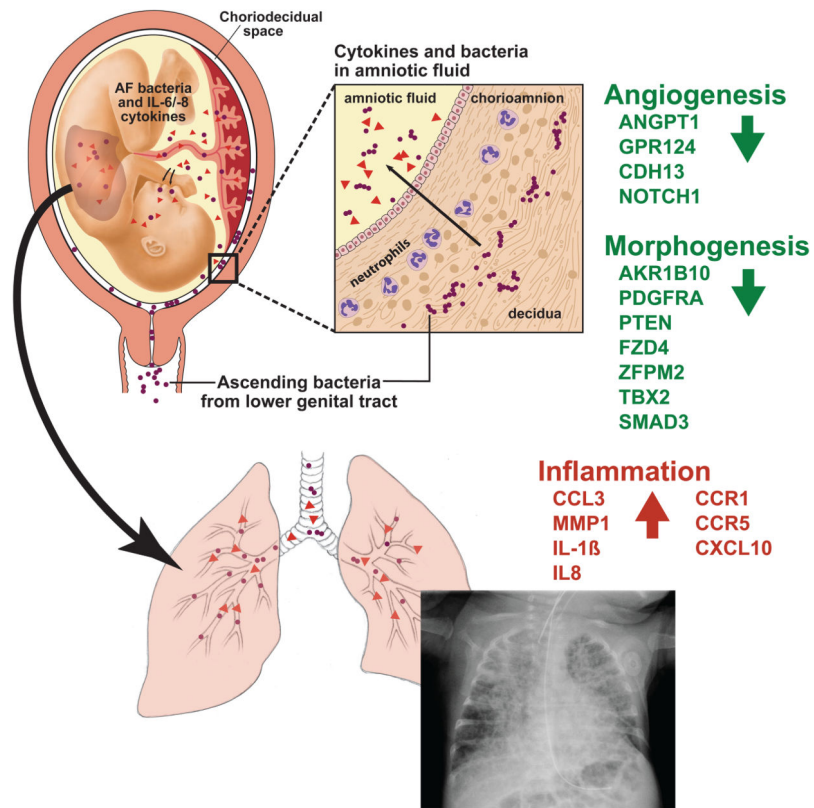
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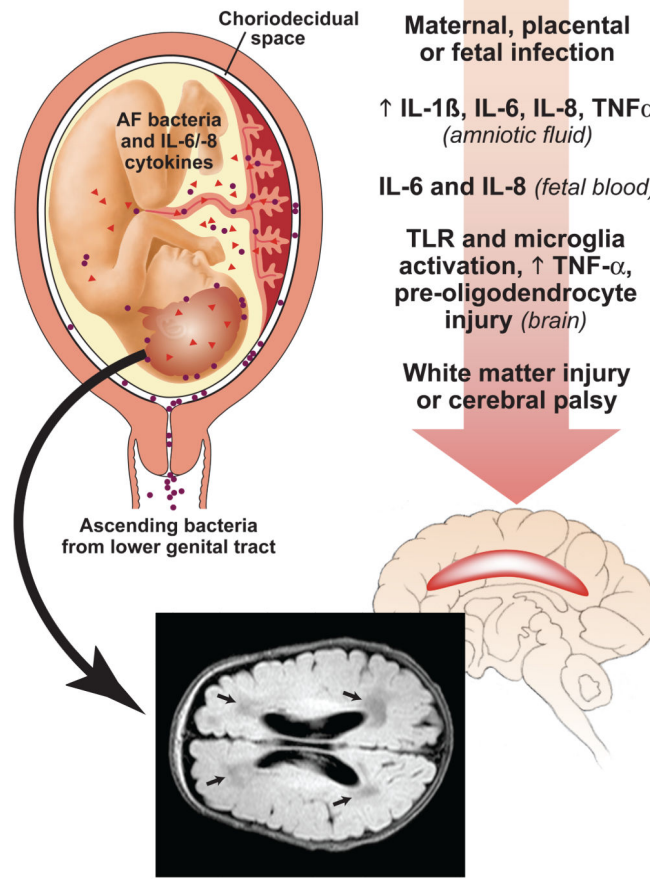


**Figure 1.**  
Bacteria, viruses and parasites known to influence fetal development





**Figure 2.** Our conceptual model of events leading to fetal lung injury *in utero*. First, bacteria from the vagina traffics into the choriodecidual space. Inflammation (e.g. IL-8 and IL-6) is produced by the decidua and/or membranes, which diffuses into the amniotic fluid and fetal lung. Fetal lung injury is induced by inflammatory mediators with significant genes shown involved in inflammation, cellular growth, and angiogenesis. IL, Interleukin; AF, amniotic fluid.



**Figure 3.**

Our conceptual model of events leading to fetal brain injury *in utero*.

Bacteria traffic from the lower genital tract into the uterus. Inflammatory mediators (e.g., IL-6 or IL-1 $\beta$ ) and/or bacteria may reach the fetal circulation directly through placental transmission into the umbilical cord or indirectly through the amniotic fluid and subsequent spread to the fetal lungs and pulmonary circulation by amniotic fluid exchange. Once bacteria or cytokines enter the blood, inflammation may result in disruption of tight and adherens junctions in the blood-brain or blood-CSF barrier leading to pathogen or cytokine trafficking across disrupted tight junctions with subsequent activation of astrocytes and microglia. The degree of gray and white matter injury depend on the extent of microglial and astrocyte activation as well as the infectious source, duration, and degree of inflammation.

Table 1

Select fetal pathogens and associated morbidity

Pathogen	Fetal Morbidity	Spontaneous abortion or fetal death
<b>Bacteria</b>		
Group B Streptococcus	Early-onset disease (<7 days): sepsis, pneumonia, meningitis, death Late-onset disease (>7 days): fever, meningitis	
<i>Listeria monocytogenes</i>	Preterm birth, chorioamnionitis, fetal distress, meconium aspiration syndrome. Early-onset disease (<36 hours after birth): sepsis, respiratory distress or pneumonia. Late-onset disease (5 days – 2 weeks postpartum): sepsis and meningitis.	yes
<i>Chlamydia trachomatis</i>	Conjunctivitis and blinding corneal injury, neonatal pneumonia, otitis media, asthma	yes
<i>Neisseria gonorrhoea</i>	Conjunctivitis and blinding corneal injury, arthritis, meningitis	no
<i>Treponema pallidum</i>	Early congenital syphilis: hepatomegaly, jaundice, hemolytic anemia, thrombocytopenia, maculopapular rash Late congenital syphilis: "saddle nose" deformity, "Hutchinson's teeth", eighth nerve deafness, mental retardation, hydrocephalus, seizures	yes
<b>Viruses</b>		
Parvovirus B19 (fifth disease)	Hydrops fetalis, anemia, cardiomegaly, pericardial effusion, fetal growth restriction, thrombocytopenia, abnormal long-term neurodevelopment	yes
Cytomegalovirus	Mental retardation, sensorineural hearing loss, preterm birth, preeclampsia, fetal growth restriction	yes
Herpes simplex virus	Encephalitis, sepsis, cataracts, pneumonitis, myocarditis, hepatosplenomegaly, chorioretinitis, encephalitis, mental retardation	yes
Varicella zoster virus (chickenpox)	Skin lesions, neurological and eye defects, limb hypoplasia, fetal growth restriction, defects of multiple organ systems	yes
Coxsackie B virus	Myocarditis, cardiac anomalies, rash, skin lesions, pneumonia, meningitis/encephalitis, increased risk of Type 1 diabetes in childhood	yes
Enteroviruses	Increased risk of Type 1 diabetes in childhood	no
Mumps virus	No increase in congenital anomalies, but elevated risk of spontaneous abortion	yes
Rubella virus (German measles)	Defects in multiple organ systems including the ophthalmic (cataracts, microphthalmia), cardiac, neurologic (deafness, mental retardation) and increased risk of Type 1 diabetes in childhood	yes
Rubeola virus (measles)	No increase in congenital anomalies, but high perinatal mortality rate and preterm birth	yes
Hepatitis B virus	Fetal and neonatal hepatitis, low birth weight	no
Hepatitis E virus	Fetal and neonatal hepatitis	yes
Japanese encephalitis	Spontaneous abortion	yes
Human immunodeficiency virus	Spontaneous abortion, stillbirth, intrauterine growth retardation, low birthweight and preterm birth, neurodevelopmental delay	yes
<b>Parasites</b>		
<i>Toxoplasma gondii</i>	Hydrocephalus, seizures, unilateral microphthalmia, eye disease, intracranial calcifications	yes

Pathogen	Fetal Morbidity	Spontaneous abortion or fetal death
<i>Trypanosoma cruzi</i>	Low birth weight, preterm labor, hepatosplenomegaly, respiratory distress, anasarca, cardiac failure, meningitis/encephalitis, progression to chronic Chagas	yes
<i>Plasmodium falciparum</i>	Fetal growth restriction, low birth weight, preterm birth, congenital malaria	yes
<i>Plasmodium vivax</i>	Fetal growth restriction, low birth weight, preterm birth, congenital malaria	yes