**Significance of the placental barrier in antenatal viral infections**

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**Abstract**:

The placenta provides a significant physical and physiological barrier to prevent fetal infection during pregnancy. Nevertheless, it is at times breached by pathogens and leads to vertical transmission of infection from mother to fetus. This review will focus specifically on the Zika flavivirus, the HIV retrovirus and the emerging SARS-Cov2 coronavirus, which have affected pregnant women and their offspring in recent epidemics. In particular, we will address how the timing of viral infection affects the immune response at the maternal-fetal interface, how the placental barrier is physically breached and the consequences of infection on various aspects of placental function to support fetal growth and development. Improved understanding of how the placenta responds to viral infections will lay the foundation for developing therapeutics to these and emergent viruses, to minimise the harms of infection to the offspring.

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**Introduction**

The placenta is a specialised organ unique to mammalian pregnancy and drives numerous physiological adaptations that occur in the mother. These adaptations are dynamic and crucial for enabling the mother to physically support the different fetal needs at various stages of pregnancy [1]. One of the key changes that occurs is in the maternal immune system. During pregnancy, multiple aspects of the maternal immune system function differently from the non-pregnant state in order to avoid unwanted rejection of the semi-allogenic fetus, while still being responsive to threats that could harm both mother and her offspring. Maternal immune cells undergo multiple temporal changes in sub-populations during gestation [2, 3], with upregulation of those involved with innate immunity [4]. The uterine immune cells, such as natural killer cells, macrophages and dendritic cells, are present in high numbers, which are necessary for the successful implantation and formation of the decidua. They also contribute to a pro-inflammatory state that supports tissue repair during trophoblast invasion in early pregnancy [5]. In mid-pregnancy, there is a shift from a pro-inflammatory (Th1) state to an anti-inflammatory (Th2) state, which facilitates immune tolerance and rapid growth of the fetus [5]. At the last stage of pregnancy, the maternal immune system again moves to a pro-inflammatory state to enable the parturition process, whereby the uterus must contract to successfully expel the fetus and detach the placenta that is no longer required [5]. The tight regulation of these immune modulations at the different stages of pregnancy, is in part, driven by the placental endocrine output [1, 2]. Hence, the placenta is undoubtedly a key player in regulating the immune response at the maternal-interface.

The placenta also serves as a physical barrier to prevent vertical transmission of infections from mother to fetus. The syncytiotrophoblast layer, which is in direct contact with maternal blood, is reasonably resistant to most pathogens, in contrast to the cytotrophoblast and other cells within the chorionic villus core that are highly susceptible to infections [6]. The placental defense system includes the production of antimicrobial factors, such as defensins and a highly complex cytoskeleton network, that serves to physically block pathogen entry [6]. Studies on murine placental models show that disruption of actin polymerisation with cytochalasin D (a potent mycotoxin capable of causing disease in humans), results in decreased syncytial elasticity and is associated with increased bacterial invasion [7]. Viral transmission may also be facilitated by mechanical stress and hypoxic injuries during pregnancy that cause shedding of syncytiotrophoblast and by immune-mediated injury from maternal antibodies [8]. Therefore, disruption of the syncytiotrophoblast barrier significantly increases the risk of vertical transmission.

Within the placenta, there is also a resident population of immune cells. The chorionic villi macrophages are known as the Hofbauer cells, which are considered of fetal in origin [9]. Macrophages are tissue-resident immune cells that have crucial immunological functions such as antigen presentation, phagocytosis, cytokine secretion, and the coordination of innate and adaptive immune responses. Hofbauer cells are commonly targets of a number of viruses and other pathogens at the maternal–fetal interface due to expression of surface proteins such as CD4 that enable cellular entry of HIV [6]. Hofbauer cells constitute a mixture of M2a, M2b, and M2c macrophages, which differ in marker surface expression, cytokine secretion and functions [10], thereby reinforcing the concept of a regulatory rather than inflammatory role of these cells. To date, there is limited information on the specific role of these cells in placental physiology; however, there have been suggestions that they may also play a role in the transmission of antibodies from the mother to fetus through the surface expression of Fc receptors [11-13].

Recent health emergencies have highlighted the vulnerability of pregnant women and their fetuses to antenatal viral infections. For instance, the case fatality rate of the 2009 pandemic influenza virus was up to around 4 times higher at 11% in the pregnant state, as compared with 2.5% in the non-pregnant state [4]. Studies suggest that immunomodulation in the pregnant state can affect viral clearance , which may constitute a compromise to prevent immune rejection of the fetus [2]. Delays in viral clearance may contribute to persistence of the infection and increase the chance for harm to both mother and child. This review focuses on significant viral infections: Zika flavivirus, HIV retrovirus and SARS-CoV2 coronavirus, which cause congenital Zika syndrome (CZS), acquired immunodeficiency syndrome (AIDS) and coronavirus disease 2019 (COVID-19) respectively. In particular, we will address how the timing of viral infection affects the immune response at the maternal-fetal interface, and how the placenta barrier is physically breached and the consequences of infection on various aspects of placental function that support fetal growth and development. Improved understanding of how these virus infections affect the maternal-fetal interface is vital to prevent detriment due to vertical transmission from mother to fetus.

**Zika virus**

The Zika virus (ZIKV) belongs the Flaviviridae family, which includes the dengue and yellow fever viruses, and is primarily transmitted by the Aedes mosquito. Although the virus was first identified in Africa in 1947, Zika infection was only recognised as a significant issue for pregnancy in 2015 due to an epidemic of Brazilian infants born with a congenital syndrome (including microcephaly) that was eventually shown to be caused by the Zika virus [14]. Vertical transmission of ZIKV can occur across all trimesters of pregnancy, regardless of whether the mother is symptomatic or not [15]. Children infected with ZIKV *in utero* may develop a range of features including brain lesions (eg. calcifications, ventriculomegaly, abnormal myelination) neurodevelopmental delay, musculoskeletal anomalies (eg. club foot, hip dysplasia, inflexible joints), congenital deafness and impaired vision [14], which diminishes quality of life. Its teratogenic effects are why increased understanding of the mechanisms underlying vertical transmission is vital.

ZIKV is able to cross the placental barrier to infect the fetus, although its ability to do so largely depends on the gestation of pregnancy. The trophoblast cells of the early developing placenta express many of the attachment factors (including AXL and TYRO3) that facilitate ZIKV entry in contrast to term placental trophoblast cells that do not, which renders the early placenta more susceptible to infection [16]. The maternal decidual cells also show a similar gestational age-dependent effect with decidual cells from early pregnancy having higher expression of ZIKV attachment factors and reduced innate immune responsiveness as compared with that from term pregnancies [17]. Moreover, *in vitro* functional studies demonstrated that secretions of ZIKV-infected decidual cells could enhance ZIKV infectivity of placental trophoblast cells [17], which may explain the variance in disease severity observed across gestation. Additionally, type I interferon, which is induced by viral infection [18], can promote expression of IFN-induced transmembrane proteins that inhibit cell fusion and renders syncytiotrophoblast less susceptible to viral infection *in vitro* [19]. However, studies in mice with altered type I interferon signalling showed that fetuses with intact signalling had more ZIKV-induced pathology than fetuses with defective signalling as a result of compromised placental development in mid-gestation [20], which suggests that gestational age may be a significant factor that determines whether type I interferon has an overall beneficial or harmful effect on placental barrier function to viral infection.

ZIKV crosses the placental barrier either by physical disruption of the syncytial monolayer or by transcytosis whereby the virus is transported across a cell in vesicles [21]. The barrier integrity of the syncytial monolayer is mediated by the extracellular matrix and intercellular junctions. The ZIKV non-structural protein 1 (NS1) component affects the integrity of ZO-1 and E-cadherin intercellular junction complexes and leads to breakdown of the extracellular matrix via increased production of hyaluronidases, which compromises the relative impermeability of trophoblast cells *in vitro* [22]. Analysis of ZIKV-infected placentas similarly demonstrated increased permeability and aberrant tight junction protein expression [23]. Such modulations are also observed for endothelial cells [24], suggesting this is one of the key mechanisms that enables the virus to cross from the placenta through fetal vasculature into the fetal circulation then to the fetal brain. Additionally, *in vitro* studies demonstrate the ability of ZIKV to breach the placental barrier by transcytosis, which can be attenuated by reducing ambient temperature or by using pharmacological endocytosis inhibitors [21]. Transcytosis of ZIKV is believed to be partly mediated by Fc receptor for IgG, which enables transfer of protective antibodies from mother to fetus. Targeting the Fc receptor with an inhibitor could block ZIKV infection in an *in vitro* placental explant model [25]. Conversely, Fc receptor-mediated transcytosis of ZIKV in the placenta could be enhanced by the presence of cross-reactive antibodies to dengue virus that belong to the same flavivirus family [25]. As such, vertical transmission of ZIKV may be enhanced in populations where dengue is endemic. Therefore, both placental barrier breaching mechanisms may need to be targeted to more effectively prevent transmission of ZIKV from mother to fetus,

Once the placental barrier is breached, the virus is able to infect multiple cell types within the placenta including the cytotrophoblast, fibroblasts, Hofbauer and endothelial cells, and enabling it to spread cell to cell to reach the fetal blood stream [26-28]. Histological analysis of second and third trimester placentas from ZIKV-affected pregnancies demonstrate that unlike other vertically-transmitted infections such as toxoplasmosis, ZIKV infection does not result in placental villitis, but instead is characterised by hyperplasia of Hofbauer cells [29]. The detection of ZIKV in Hofbauer cells up to ten weeks following maternal infection suggests that Hofbauer cells play a key role in vertical transmission [30]. The placenta may thus also serve as a reservoir for ZIKV infection to persist throughout the pregnancy. Indeed, replicating ZIKV was detectable in the human placenta from the first and second trimesters [31]. This ability to replicate within the placenta could prolong the infection and have a greater impact on the pregnancy outcome.

Endothelial cells are the last component of the physical barrier before viral entry into the fetus. AXL and its ligand Gas6 enables ZIKV to more efficiently infect endothelial cells compared with the closely related dengue and West Nile viruses [32]. Infection of the endothelial cells results in increased production of matrix metalloproteinases, pro-inflammatory cytokines and tissue factor, which associates with greater permeability, thrombin generation and apoptosis of the endothelial cells, *in vitro* [33, 34]. These detrimental effects on endothelial cells are consistent with impaired angiogenesis shown in the placentas, brains and retinas of an *in vivo* mouse model of ZIKV infection [35]. Such vascularisation defects would compromise nutrient supply, which is necessary for proper organ growth and development and could partly explain the neuronal damage and microcephaly, as well as the increased risk of intrauterine growth restriction, abnormal umbilical artery Doppler waveforms and perinatal detah, seen in ZIKV-infected fetuses in humans and various animal models [14, 35-37].

ZIKV infection greatly affects placental function. Infected first trimester trophoblast cells have decreased cell migration, impaired lipogenesis, mitochondrial dysfunction and an altered immune tolerance secretory profile, which may have detrimental consequences for placentation [38, 39]. Even at term, the transcriptomic hallmarks of mitochondrial dysfunction were detectable in a placenta of an infant exposed to ZIKV infection in the first trimester [40]. The response to infection is also dependent on host genetics. Transcriptomic analysis of twins disconcordant for ZIKV infection revealed that following ZIKV infection *in vitro*, stem cell-derived trophoblast cells of affected twins had impaired activation of the immune response and downregulation of key cell adhesion genes as compared to that of unaffected twins, which likely influenced their susceptibility to infection [41]. A better understanding of the factors regulating susceptibility may allow us to identify targets to modulate the consequences of infection and improve outcomes of ZIKV-affected pregnancies.

**Human immunodeficiency virus**

Human immunodeficiency virus-1 (HIV) is a lentivirus that attacks the human immune system and if left untreated, results in AIDS. HIV infection remains a global health problem with 38 million people worldwide living with HIV and 1.7 million newly infected patients in 2019 [42]. Transmission from mother to her offspring accounts for most childhood HIV infections and may occur through the following mechanisms: *in utero* transplacental transport during second and third trimesters of pregnancy, intrapartum transmission during labour and delivery, or infection through breastfeeding.

The placenta provides an efficient but not absolute barrier to HIV vertical transmission. The mechanisms of viral transport are not fully described but most likely, HIV crosses the placenta through breached villous surface; vertical transmission through CD4+ endothelial tissues or CD4+ Hofbauer cells has also been reported [43]. Transplacental transport of HIV-1 is associated with altered expression of various cytokines such as leukemia inhibitory factor, IL10 and IL4, and chemokine receptors including CCR5 and CXCR4 [44, 45]. Hofbauer cells may prevent mother to child transmission of HIV-1 by the induction of immunoregulatory cytokines, which highlights these macrophage cells as important mediators of fetal protection during HIV-1 exposure [46]. The placenta may also maintain its immunological potential against HIV infection by increased expression of innate immunity factors [47]. However, the exact role of these factors in controlling HIV-1 transmission and infection of trophoblasts remains to be elucidated. HIV can infect and replicate in the placental trophoblast cells, allowing them to serve as viral sanctuary sites [43]. Subsequently, even when treated with antiretroviral therapy, HIV is able to survive in the placenta at low levels and may reactivate if treatment is terminated [48].

Antental HIV infection is undoubtedly detrimental for fetal growth and development. Intrauterine infection with HIV is associated with increased frequencies of spontaneous abortion and stillbirth, as well as higher perinatal and infant mortality rates, [49-51]. Moreover, HIV-exposed fetuses are at higher risks of prematurity, intrauterine growth restriction, and low birth weight [51], which can lead to early infant mortality and chronic diseases later in adulthood [52, 53]. Other factors such as social vulnerability, poverty, and substance abuse may serve to exacerbate these risks [51, 52]. Although overt examination of the placentas from HIV-infected women show no major morphological abnormalities in all 3 trimesters, placentas are typically lighter with regions of inflammation and necrosis at the macroscopic and microscopic levels [50, 54, 55], which would compromise placental function and contribute to impaired fetal growth or intrauterine death due to insufficient nutrient supply.

Nonetheless, over the last three decades, we have witnessed a tremendous success in reducing materno-fetal transmission of HIV to less than 1%, preventing infection of an estimate of 1.4 million children between 2010 and 2018 [56]. Prevention of materno-fetal transmission consists of four main parts: 1) maternal testing and prenatal counselling, 2) administration of antiretroviral therapy during pregnancy, labour, and delivery, followed by postnatal administration to the infant, 3) elective caesarean delivery before amniotic membrane rupture if HIV load is high or unknown and 4) avoidance of breastfeeding. Currently, over 30 FDA-approved antiretroviral drugs are available to treat HIV-positive patients, in monotherapy or combinations; nine of which are prescribed to pregnant HIV-positive women. Although the effect of antiretroviral therapy is undeniable, their pharmacokinetics, pharmacokinetics and toxicity in pregnancy remains to be properly elucidated*.*

**Severe acute respiratory syndrome coronavirus 2**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused the COVID-19 pandemic, is an enveloped single positive stranded RNA virus that has affected over 120 million people worldwide within one year [57]. Pregnant women and their developing fetuses may represent a high-risk group [58, 59], although this point remains controvesial as there is debate about whether pregnant women fair more poorly compared with non-pregnancy women of similar demographics. While other coronavirus-associated diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) that are caused by SARS-CoV-1 and MERS-CoV, respectively have severe effects on both the mother and the fetus, the effects of COVID-19 on pregnancy appear to be milder [60]. Universal screening of pregnant women who were admitted to hospital for delivery during the COVID-19 epidemic in the UK showed that about 15.4% of these women were positive for SARS-CoV-2, and among these, 87.9% were asymptomatic [61]. A systematic review showed that approximately 3.2% of neonates born to mothers with COVID-19 had positive nasopharyngeal swabs around the time of birth, suggesting that vertical transmission of SARS-CoV-2 is possible, but not common [62].

SARS-CoV-2 is cannonically thought to gain entry using the host cell receptor angiotensin converting enzyme 2 (ACE2) and the serine protease TMPRSS2 [63, 64]. Nevertheless, the human placenta appears to have variable expression of these two genes between subjects [65-67], which may explain the few possible cases of vertical tranmission reported [62]. Moreover, placental syncytial absence of caveolins, which is sometimes involved with viral entry, may serve as an additional physiological defence mechanism to prevent vertical tranmission of SARS-CoV-2 [68]. A preliminary bioinformatics study suggested that other factors with increased expression in the placenta such as DPP4 and CTSL, could instead be what mediates SARS-CoV-2 entry into placental cells to affect the conceptus [69]. Furthermore, the low levels of reported viraemia may also contribute to reduced vertical transmission, given that the virus needs to circulate in the maternal blood to reach the placenta [70]. Analysis of placentas from COVID-19 affected women showed detectable levels of viral RNA and protein in villi only in a subset of placentas [67, 71], highlighting that while SARS-CoV-2 can infect the placenta and may associate with intervillositis and syncytial necrosis [72], this occurs rarely.

Investigation of the possible molecular mechanism(s) of SARS-CoV-2 vertical transmission at the maternal-fetal interface during pregnancy is ongoing. The maternal-placental interface with its unique immune cell distribution may provide a modulatory immune defense with a trophoblast-immune cell crosstalk. We propose that in response to SARS-CoV2 infection, placental cells may secrete increased pro-inflammatory cytokines, which in turn could modulate the expression of key inflammasome machinery including NLRP3 and trigger dysregulated activation of the intracellular cysteine protease, caspase-1 and secretion of the cytokine, interleukin 1 (IL-1) as illustrated in Figure 1. As IgG antibodies are known to transfer across placenta starting from the mid-trimester of pregnancy with increasing transmission over time, detection of SARS-CoV-2 specific IgG antibodies in cord blood at birth is not unexpected in neonates born to women with antenatal infections [73, 74]. However, a class of larger, pentameric antibodies (IgM) which are produced in an acute phase of an infection are not known to cross placenta. Hence, the presence of SARS-CoV-2 specific IgM antibodies in cord blood provides some evidence for vertical transmission in rare cases [75], nonetheless there remains debate about the specificity of the IgM tests conduced. Therefore, more definitive evidence for vertical transmission via the placenta is still required [76], and further studies are encouraged to resolve this issue.

SARS-CoV-2 infection can compromise placental function and contribute to poor pregnancy outcomes. An in-silico based approach comparing the SARS-CoV-2 human interactome and differential expression analysis of genes associated with critical placental functions predicts that key trophoblast functions such as invasion, differentiation, maturation, spiral arteriole remodeling may be affected by SARS-CoV-2 infection and lead to defective placentation [77]. Given the consequential inflammatory signalling cascade as a result of infection, the fact that SARS-CoV-2 can also infect and replicate in endothelial cells (such as that of umbilical vessels) and the presence of Ang-(1-7) as well as ACE2 enzyme in the placenta including the synctiotrophoblast, villious cytotrophoblast, invasive/intravascular trophoblast, decidual cells, and vascular smooth muscle cells; vascular function may be compromised in pregnancy [78]. Indeed, although several studies report few histopathological differences in the placentas from infected women and controls [79-81], other morphological studies of placentas from women infected in late pregnancy showed decidual arteriopathy, maternal vascular malperfusion, fetal vascular malformations and malperfusion [82, 83], massive systemic inflammation characterised by the presence of M2 macrophages, cytotoxic and helper T cells, activated B lymphocytes along with fibrin deposition; which may contribute to the increased risks of pre-eclampsia, preterm birth and stillbirths demonstrated in a meta-analysis [84]. To date however, there is limited data on the effect of first trimester SARS-CoV-2 infection on the pregnancy outcome. An initial report suggests that COVID-19 does not increase the risk of spontaneous abortions [85], but the longer term consequences on a continuing pregnancy remains to be investigated. Therefore, as COVID-19 is a newly identified disease, many studies of COVID-19 in pregnancy and its longer-term consequences are still required for better understanding.

**Gaps in the existing literature**

While much research is ongoing to understand the mechanisms of vertical transmission from mother to fetus, there remains multiple gaps in the knowledge behind these viral infections including how pre-existing maternal health influences disease trajectories, significance of possible co-infections and the longer term consequences of antenatal viral infection and treatment. For instance, it is still unclear what drives disease severity of each infection, why some fetuses appear more vulnerable to *in utero* infection than others and how it is possible for an asymptomatic mother to have a severely affected fetus in the case of ZIKV infection [14]. Nevertheless, although the Zika epidemic appears to have subsided, more than 2 billion people live in areas where the Aedes mosquito can breed and future outbreaks may still occur [14]. Moreover, the HIV and COVID-19 pandemics remain ongoing and continues to affect millions. Therefore, further studies are encouraged to answer existing gaps to protect pregnancies and improve offspring health in the long term.

*How do current anti-viral therapeutics affect the placenta and programming of offspring development?*

While anti-viral therapeutics may effectively treat the underlying viral infection, there may be unintended effects on the pregnancy. For instance, some evidence suggests that HIV antiretroviral therapy (ART) contributes to placental dysfunction and maternal endothelial dysfunction, which could predispose a pregnant women receiving HIV ART to developing pre-eclampsia [86]. Known effects of anti-viral therapeutics on the pregnancy *in vivo* and the placental trophoblast *in vitro* are summarised in Table 1. HIV-positive women treated with integrase strand transfer inhibitor-containing combinations had higher rates of hypertensive disorders of pregnancy than those treated with protease inhibitors [87]. However, those who received ART with protease inhibitor-containing combinations, particularly from preconception, had higher rates of preterm deliveries and low birth weight infants [88]. *In vitro* studies suggest that protease inhibitors may disrupt decidualisation and spiral artery remodelling, which are critical processes for adequate placentation, and contribute to poor pregnancy outcomes [89]. Such adverse pregnancy outcomes are also associated with detrimental consequences on postnatal offspring life [53] and should be taken into account when deciding on the most optimal anti-viral treatments to be used during pregnancy. Nevertheless, it is clear that in the case of ART for HIV positive mothers, the benefits of reducing vertical transmission of HIV to the fetus to prevent death early in childhood from AIDS greatly outweighs the risk of programming effects that manifest much later in life.

In a pandemic situation however, given the urgent need to find treatments, drugs are sometimes repurposed, with some HIV anti-virals being trialled for use in the COVID-19 pandemic [86]. Notwithstanding the limitations of current studies that use clinical observations derived from case-control analysis; *in vivo* animal models that may not capture human pregnancy in its entirety; and *in vitro* models that may not fully reflect the complex interplay between mother, placenta and fetus [90]; such studies are still important in demonstrating how anti-virals affect maternal-placental-fetal unit, so that clinicians can make proper informed judgements about the most suitable therapeutics to use, particularly in a desperate situation such as a pandemic.

*Sex differences in placental response to viral infections*

Additionally, sex is emerging as a potent modulator of the placental response [91]. Multiple studies demonstrate sexual dimorphism of the placental transcriptome, with reported enrichment of pathways involved with the immune system and inflammatory pathways in male placentas that may explain increased pregnancy complications with male fetuses [92]. Indeed, a porcine model of antenatal ZIKV infection demonstrated that male placentas had more differentially expressed genes than female placentas in response to infection, which were subsequently associated with differential offspring behaviour in a stressful environment [93]. Furthermore, a mouse model of ZIKV infection showed males to be more susceptible to intrauterine death and neuronal defects, which suggests that sex-specific responses to infection may drive differential outcomes between the sexes [94]. However, to date, no published studies have examined the sex-specific placental responses for HIV or SARS-CoV2 infections. Hence, future studies should also consider sex as an important factor in understanding the mechanisms and consequences of antenatal viral infections.

**Conclusion**

Improved understanding of how the placenta responds to viral infections will lay the foundation to developing therapeutics to emergent viruses in the future to minimise the harms of infection to cause fetal demise or poor long-term health outcomes.

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