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Review of Viral Infections in Pregnancy Placental Immunity Vertical Transmission and Adverse Outcomes

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Abstract
This review will focus on the effects of viral infections in pregnancy. Throughout gestation, viral infections are known to lead to adverse events including mortality of the fetus and mother, premature birth, miscarriage and congenital anomalies. The intricate immunological environment of pregnancy requires a fine balance in which the placenta must accept exposure to some allogeneic fetus while protecting against pathogens. Even though natural defense in the maternal-fetal interface prevents viral transmission, some viruses hijack poorly understood mechanisms that disrupt the integrity of the placenta, leading to vertical transmission and this can have severe consequences on fetal health. This review highlights the intricate relation of main viruses with pregnancy, including mechanisms in pathogenesis as well as maternal-fetal complications, and the cell and molecular substrate for trans placental infection. Key features of placental immune protection are trophoblast cells, innate immune populations, cytokine control, pathogen recognition and antimicrobial products, all being essential in preparing for new emerging challenges to the pregnant population.
Keywords: Vertical transmission; Placental immunity; SARS-CoV-2; Zika virus; HIV; Influenza A; Congenital disease; Hepatitis B; Trophoblasts

1. Introduction

Viral infection effects in pregnancy on the health of the mother as well as the foetus have been brought to attention following recent viral outbreaks such as ZIKV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pregnancy is characterized by specific physiological modifications, mainly of hormonal and immune nature; such changes predispose the pregnant population to be more susceptible to microbial attacks and, for this reason, they are at higher risk for unfavorable effects [1]. These include maternal morbidity, spontaneous foetal loss, IUGR, preterm birth and foecal demise as well as other congenital anomalies.

Considering the lack of safe antiviral remedies and vaccine options in gestation, this population may potentially have an increased susceptibility to the deleterious effects of viral pathogens [2]. During pregnancy, the placenta—a temporary, but indispensable organ—supports fetal growth and development, while serving a dual immune function; it allows tolerance to the semi-allogeneic fetus as well as protection against infectious danger. This immunological balance is necessary for fetal survival in the face of continuous microbial exposure [3].

Despite the strong defense that has been developed by the placenta, it is worth noting that some of the viral pathogens have evolved mechanisms over time to exploit these types of defenses and bypass them for the purposes of vertical transmission at a cost detrimental for the mother. Though classical

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TORCH pathogens (toxoplasmosis, rubella, cytomegaloviruses and herpes simplex virus) were well described for their vertical transmission. How emerging/re-emerging viruses overcome placental defense is largely elusive. Less is known about mechanisms where new or re-emerging viruses evade placental defenses [4].

In the present review, we describe the biological behavior and pathogenic potential of some well-known or emerging viruses (HBV, HIV, IAV, ZIKV, SARS-CoV-2) that have been related to pregnancy complications [5]. In this review, the implications of viral infections in relation to fetal and maternal outcomes during pregnancy and their mode of vertical transmission along with the placental immune response against them are indicated (Fig. 1). These results underscore the necessity for an extensive discussion of the mechanisms of virus entry and its implication in both the generation and discovery of potential anti-viral drugs [6].

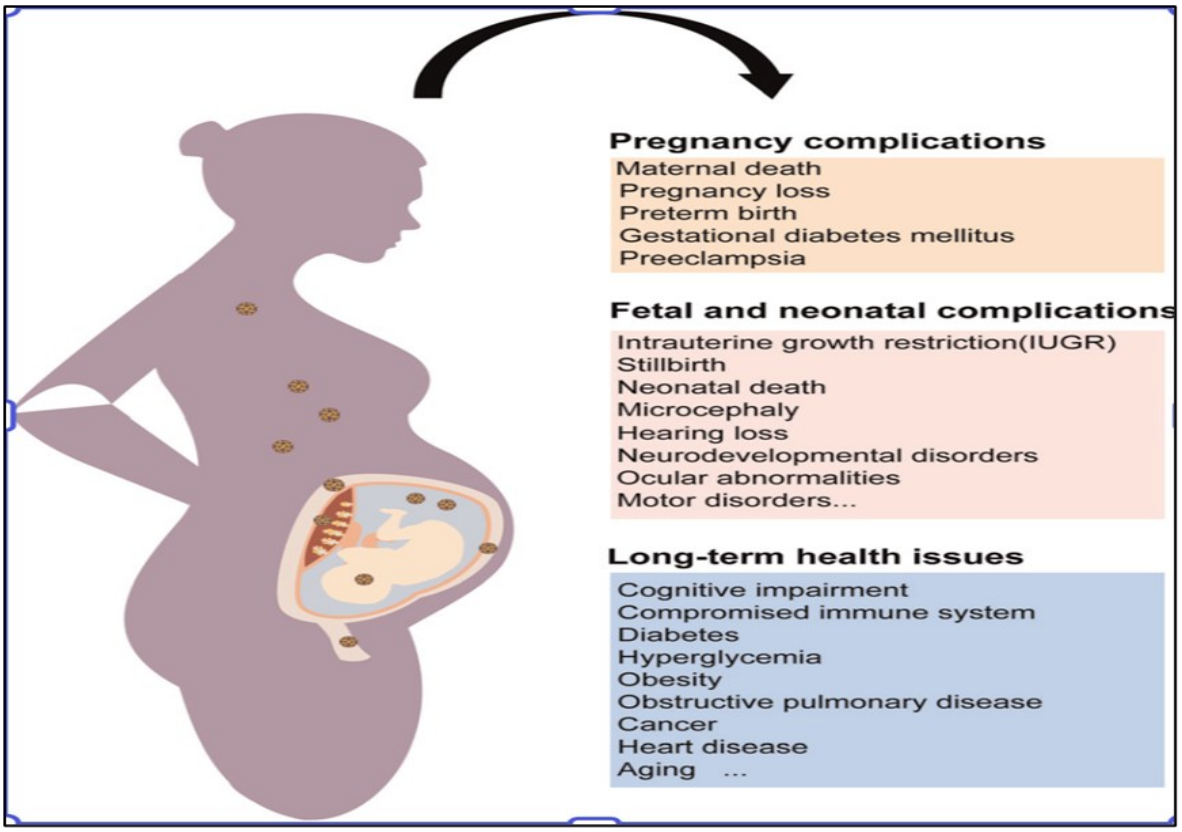

Fig. 1 Maternal-Fetal Consequences of Viral Infections during Pregnancy.

Pregnancy causes a number of physiological alterations, the most notable of which are hormonal and immunological. These alterations make pregnant women easier targets for microbial pathogens, including those of viral origin. The maternal immune response must find a balance between tolerating the semi allogeneic fetus and defending itself effectively against invading micro-organisms [2]. This immunological compromise is largely mediated by the placenta. It enables the transfer of nutrients and antibodies, and functions as a selective barrier to pathogens. This immune modulation is frequently characterized by a suppressed cell-mediated immune response, impaired NK cell activity and augmented humoral immunity. Such changes are associated with increased susceptibility to viral illness and possibly affect the severity and response of maternal-fetal disease [5]. It is crucial to understand these immune adaptations for the interpretation of the pathogenesis of viral problems during pregnancy and to develop interventions that are protective against both maternal and fetal health [8].

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2. Types of Viral Infections Affecting Pregnant Women

2.1 Hepatitis B Virus (HBV) and Pregnancy

Chronique infection is a result of the DNA virus Hepadnaviridae, and one of the most prevalent bloods borne pathogens in the world. Infected humans exhibit acute and chronic hepatitis [8]. Modes of Transmission: Infection is transmitted by exposure to infected blood and body fluids, sexual contact, parenteral exposure and vertical transmission. Perinatal transmission plays a critical role in developing chronic HBV infection, particularly among women with high viral loads or positive hepatitis B s antigen [9]. Without timely post-natal immune prophylaxis with HBV vaccine and hepatitis B immunoglobulin, the risk of infant infection may reach 90% [10].

This underscores the significance of standardized pregnancy screening protocols, which include detecting surface and e antigens, levels of viral DNA, along with liver enzyme profiles for mitigating the transmission risk [11]. Even though people worldwide are working to eradicate HBV with the use of birth-dose vaccination and antiviral treatments for the mothers, vertical transmission is still happening in many areas due to the fact that vaccine coverage is not always consistent and prophylaxis sometimes fails. HBV continues to be a significant issue in maternal-fetal health, particularly in endemic regions [12]. While complications during pregnancy related to HBV are typically considered minimal, observational studies indicate possible associations between the chronic infection and gestational issues, like premature labor, diabetes, antepartum hemorrhage, in addition to hypertensive disorders [13]. For example, the meta-analyses have linked the maternal HBsAg seropositivity to higher rates of preterm birth, although such a result is inconsistent, potentially because of coexisting hepatic conditions like nonalcoholic fatty liver disease. Notably, a twofold increase in antepartum hemorrhage has been observed among infected women, potentially resulting from coinfections or placental complications such as placenta previa and placental abruption. Paradoxically, some reports suggest HBV infection may confer a reduced risk of preeclampsia, though underlying mechanisms remain speculative [14].

With the attempts of HBV eradication strategies through birth-dose vaccination and maternal antiviral therapies, vertical transmission persists in several places because of occasional prophylaxis failure and inconsistent vaccine coverage. HBV is still a critical concern in maternal-fetal wellness, particularly in areas where it is endemic. Although HBV-related pregnancy concerns are scarce with cohort research has identified a prospective correlation between chronic infections as well as gestational disturbance, like premature labor, diabetes, hypertensive disorders, along with antepartum hemorrhage [13]. Meta-analyses have correlated maternal HBsAg seropositivity with increased preterm birth rates. Yet, there are conflicts in the results because of the coexisting hepatic conditions, like non-alcoholic fatty liver disease. A two-fold increase in the antepartum hemorrhage was indicated in infected women, possibly caused by coinfections or placental complications, like placental abruption as well as placenta previa. A few studies indicate that HBV infection might confer a decreased preeclampsia risk, although the underlying mechanisms are speculative [14]. Preliminary data also point to possible fetal and neonatal risks. Meta-analysis of more than 7,000 HBV-infected pregnancies found a higher risk of abnormal fetal heart rate tracings, perinatal asphyxia and an alteration in birth weight (from low birth weight to macrosomic). This may be due to different reasons, such as viral genotype, maternal liver condition, other infections, or the stage of the disease during pregnancy [15].

Vertical pathways of transmission include intrauterine infection and intrapartum exposure, followed by postnatal transmission through breastfeeding. The intrapartum period seems to be particularly risky as that is when the neonate is exposed to the maternal blood and secretions at birth. In addition, some studies have shown a direct infection of placental cells (trophoblasts and

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endothelial cells) by HBV, which would point to a possible pathway for transplacental transmission [16]. Although maternal antiviral treatment renders efficiency in almost eliminating vertical transmission, the precise degree and mechanism of intrauterine infection remain to be elucidated. Overall, a better understanding of the dynamics of intrauterine transmission and inadequacies of existing prophylactic interventions is essential for optimizing maternal treatment approaches and guiding strategies for global control of HBV, as demonstrated in Fig. 2. Meanwhile, the long-term safety of antiviral use in pregnant women should be further assessed to guarantee maternal and neonatal health in the future [17].

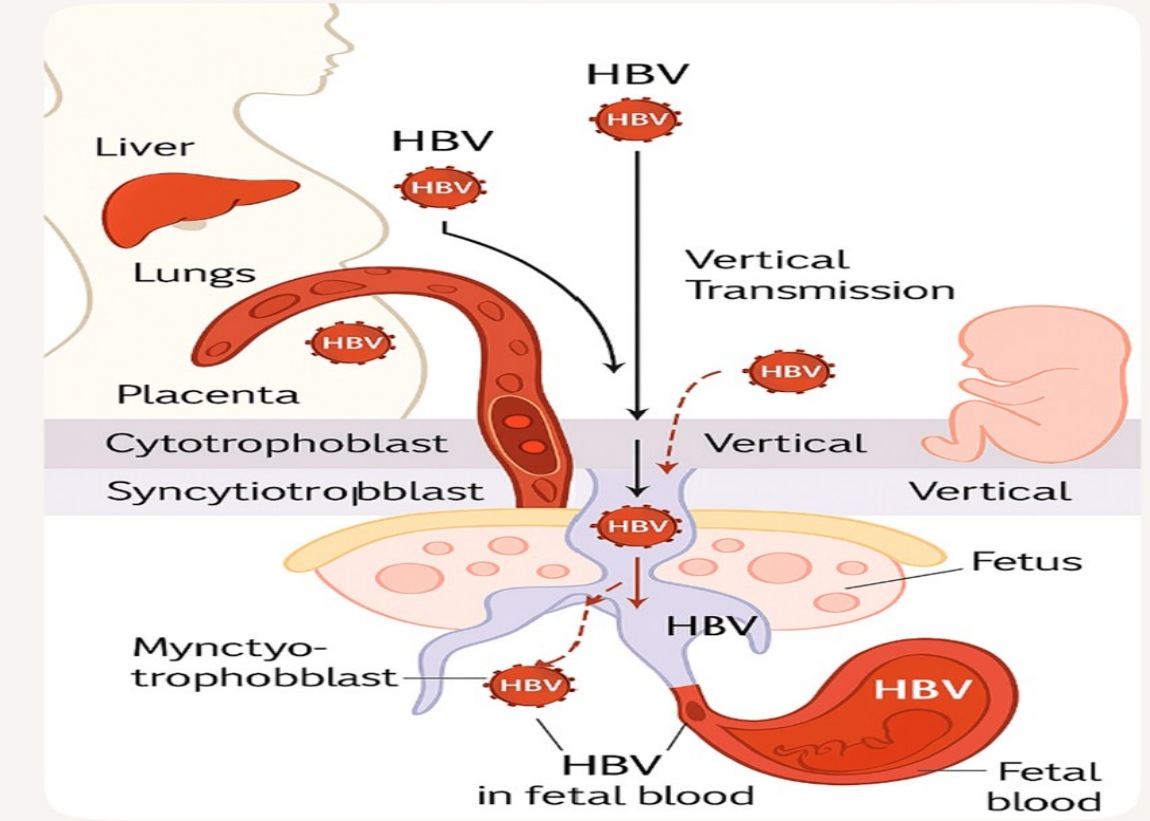

Fig. 2 Vertical Transmission of Hepatitis B Virus: Placental Crossing Mechanism

2.2. Human Immunodeficiency Virus (HIV) and Pregnancy

HIV exists in 2 main types: HIV-1 and HIV-2, which cause progressive immune system destruction resulting in AIDS. Of these, HIV-1 is the most transmissible and pathogenic and is therefore the main topic of discussion [18]. Pregnant women with HIV-1 suffer from obstetrical complications that include spontaneous abortion, preterm delivery and intrauterine growth restriction (IUGR). These effects are particularly profound among immunosuppressed or late-stage disease women [19]. The main vertical transmission pathways for infectious diseases can be divided into three modes: intrauterine exposure in gestation, exposure to genital secretions and maternal blood during delivery, along with postpartum transmission during breast-feeding. This risk is influenced by several factors, including maternal viral load, immune competence, nutritional status and the method of delivery [20].

Thorough clinical management, which includes elective caesarean section, combination anti-retroviral therapy, neonatal antiviral prophylaxis and formula feeding, has led to significant decreases in vertical transmission rates from approximately 40% to <1 %. However, despite such a success, the exact modes of mother-to-child transmission of HIV, particularly intra-uterine, are not completely clear [21]. Although the majority of utero transmissions have been in the third trimester, early fetal infection that was detected as early as eight weeks of gestation indicates the possibility that the virus

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can cross through placental barriers earlier in pregnancy than previously thought. While initial hypotheses suggested amniotic fluid as the main route of fetal HIV-1 infection through mucous absorption, new studies have been unable to isolate even simpler particles in the amniotic fluid, including those from mothers with high viremia [22].

The hypothesis of transplacental transmission is further supported by the demonstration of HIV-1 in placental tissues from infected fetuses. HIV is able to directly enter trophoblasts through a syncytia-mediated entry mechanism; however, entry of the virus into these cells is not particularly effective as compared with that for CD4+ lymphocytes. Interestingly, HIV has been found in Hofbauer cells, specialized placental macrophages expressing repertoire HIV entry co-receptors such as CD4, CXCR4, and DC-SIGN. Furthermore, the Fc gamma receptors on these cells could mediate in utero transmission through the endocytosis of HIV-antibody immune complex. This observation is consistent with the mechanism of transcytosis as an additional means for fetal infection [23]. The effect of HIV on placental structure and efficiency is also likely to result in poor pregnancy outcomes. Histopathology studies have demonstrated decreased placental weight, maternal vascular under perfusion, inflammation lesions, including chorioamnionitis and pervasive placental inflammation with HIV as demonstrated in Fig. 3.

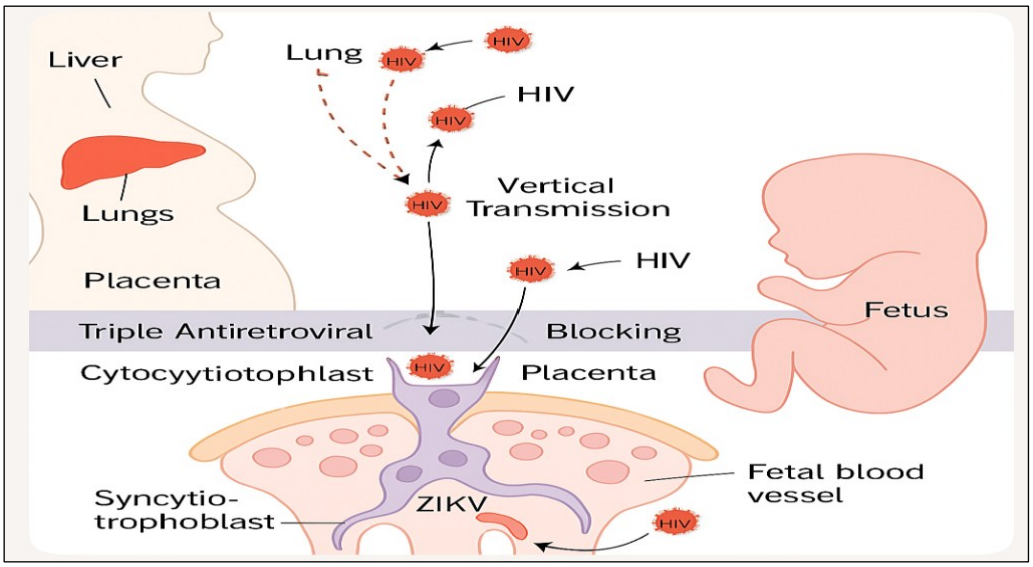

Fig. 3 HIV Vertical Transmission and Placental Défense.

Recent data suggest a 2.2-fold higher rate of maternal vascular malperfusion in HIV infected gestations, which has been associated with suboptimal fetal outcomes like Intrauterine Growth Restriction and stillbirth [24]. Furthermore, abnormal immune responses at the maternal-fetal interface are associated with fetal development impairment. Changes to the decidual T-cell population, in particular an increase in pro-inflammatory TNF-α-producing subsets, have been reported during HIV positive pregnancy. NK cell dysfunction, involving decreased activation and abnormal accumulation, could impair placental vascular development and nutrient transfer with consequent implications for fetal growth patterns [25].

The decrease in HIV vertical transmission can be attributed to the advent of cART, which has been instrumental in minimizing maternal viral load and preventing infection in the infant postnatally. Such regimens are targeting different stages of the viral life cycle, such as the inhibition related to reverse transcriptase, protease, integrase enzymes and co-receptor-mediated entry. Nonetheless, cART is not without risks: its use has been associated with higher rates of preterm delivery and complications [26].

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The etiologies of these negative effects, which include: 1) hormonal disruption - some antiretrovirals (e.g., Ritonavir) may cause lower levels of key pregnancy hormones progesterone and estradiol with associated increased risks for preterm labor and IUGR; 2) transplacental drug transfer - certain agents may have direct fetal toxicities that are systemic in nature similar to those seen in adults, or; 3) immune dysregulation long-term therapy could influence the mechanics between the maternal-fetal interface leading to early labor. Taken together, these results further emphasize the balance of care in HIV during pregnancy. While cART is essential, the appropriate safety profile should be continuously re-evaluated, which should concern both maternal and fetal outcomes [27].

2.3. Influenza A Virus (IAV) and Pregnancy

The influenza viruses are well-recognized respiratory pathogens, leading to symptoms of fever, malaise and cough. Only category A viruses like H1N1, which tend to infect people from several different species (including humans), are capable of causing a severe pandemic. Transmission is predominantly by airborne droplets, but indirect contact with mucous membranes, infected fluids and surfaces is an additional route of viral transmission [28]. Although most cases of H1N1 infection are mild, self-limited disease in the general population, in both chronic illness and those aged more than 60 years, morbidity and mortality can increase. Pregnant women are especially susceptible, with infection rates four- to five-fold greater than that of the general population and an increased risk for non-respiratory complications. In the 2009 pandemic, pregnant women had higher than expected hospitalization rates, which correlates with historical pandemics where there was significant maternal morbidity, such as in the 1918 influenza pandemic, wherein maternal mortality rates ranged between 27% and 45%, but stillbirth estimates were almost up to 52% [29]. The outcomes related to influenza are also more severe at a more advanced gestational age. Patients in their third trimester of pregnancy have been up to five times more likely to be hospitalized than patients who are in early pregnancy or postpartum. Late-trimester was also found to be a risk factor for developing cardiac and pulmonary complications. In the presence of comorbidities including obesity, metabolic impairment, cardiovascular disease, respiratory afflictions and tobacco use, severity is added to the risk associated with life-threatening flu complications in pregnancy [29].

The underlying mechanisms resulting in increased susceptibility of pregnant women to IAV is still not fully understood. Pregnancy is naturally accompanied by immuno-modulations, such as NK cells' altered activity, suppressed cell-mediated responses, along improved hormonal immunity. The reduced interferon from maternal mononuclear cells in response to IAV infection likely allows increased susceptibility to viral spread. Furthermore, incomplete activation of lung dendritic cells and impaired CD8+ cytotoxic T cell recruitment could result in a compromise to viral clearance in pregnant individuals infected by the virus [30]. Physiological alterations during pregnancy, especially cardiopulmonary adaptation, worsen the severity of the disease. Increased oxygen requirements of pregnancy and decreased lung volumes, respiratory reserve to pregnant women from resulting able to tolerance of pulmonary result better results, in an increased risk for hypoxia and decompensation with influenza [31].

Fetal and neonatal outcome after infection. Complications are IUGR, prematurity, neonatal death and potential neurological defect. Unlike TORCH pathogens, IAV rarely can cross the placenta; however, a few avian viruses (e.g., H5N1) have been detected in fetal and placental tissues as shown in Fig. 4. The indirect consequences of maternal infection, like febrile disease, systemic inflammation and hypoxia, are thought to negatively influence fetal growth. For instance, various studies have discovered that a maternal influenza infection can stimulate a systemic "vascular storm" leading to an increase in pro-inflammatory and antiviral mediators. This cascade of inflammation may interfere with placental oxygen exchange, causing hypoxic damage in both the placenta and fetal brain [32].

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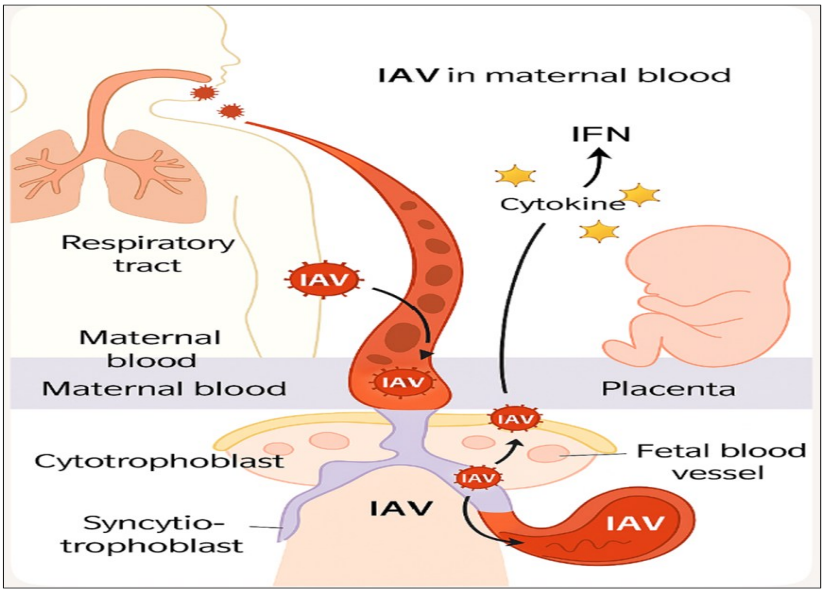

Fig. 4 Influenza A Virus Infection during Pregnancy.

There are more worries going beyond the perinatal period. Children born to mothers infected with IAV throughout pregnancy face increased subsequent disorder risks, like autism spectrum disorders (ASD). Such results are corroborated through animal models, indicating that the in-utero infection with IAV induces long-term modifications in the neural architecture as well as behavioral consequences, seemingly attributable to hypoxia, cytokine imbalance, along endocrine profiles disruption. Children born to mothers who are infected with IAV demonstrate compromised hematopoietic maturation as well as immuno-dysregulation, resulting in increased vulnerability to infectious pathogens throughout the neonatal period. The results highlight the imperative for a comprehensive mechanistic study to clarify the ways in which IAV compromises fetal and maternal health and for the purpose of identifying strategies to prevent such disruptions in high-risk pregnancies [33].

2.4 Zika Virus (ZIKV) and Pregnancy

Zika virus (ZIKV) can be defined as one of the flaviviruses, which is a single-stranded RNA virus and has been identified initially in a rhesus macaque in the country of Uganda. ZIKV experienced a rapid spread on several continents between 2015 and 2016, which prompted the World Health Organization to declare a Public Health Emergency of International Concern. This name was adopted after there was evidence that the ZIKV infection was associated with serious neurological sequelae, including Guillain-Barr syndrome in adults and congenital microcephaly in newborns [34]. While ZIKV was initially recognized as a mosquito-borne infection primarily transmitted by Aedes species, subsequent data have confirmed alternative routes of transmission, including sexual contact, blood transfusion, and, notably, vertical (mother-to-fetus) transmission.

Similar to other arboviruses, ~80% of Zika virus infections in the general population are asymptomatic. Symptomatic patients usually have vague symptoms—fever, joint aches and malaise. The estimated mortality risk is low (approximately 0.01%), and the deaths have mainly involved immunosuppressed individuals, with their distribution as indicated in Fig. 5. Pregnant women infected with ZIKV generally have symptoms similar to those in non-pregnant without consistent evidence regarding increased maternal pathogenicity. However, the consolidated clinical and experimental findings allow us to identify congenital ZIKV infection as a major cause of pregnancy disorders, including spontaneous abortion, IUGR, preterm delivery, foetal death [35].

There is high importance in recognizing the Congenital Zika Syndrome (CZS), which is considered a group of symptoms describing functional and structural problems in neonates and

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fetuses after intrauterine ZIKV exposure. No less than 4,000 cases of CZS were indicated in labs globally. Also, the syndrome usually includes brain problems (like subcortical calcifications and ventriculomegaly), severe microcephaly, in addition to ocular problems. Brazilian cohort study identified brain calcifications (93%) in the microcephalic babies with confirmed exposure to ZIKV, succeeded by cortical malformations—lissencephaly (69%) as well as ventriculomegaly (66%). Other ocular manifestations, including chorioretinal atrophy, optic nerve hypoplasia, cataract, along with loss of foveal reflex, were noted in about 35-70% of the cases [36].

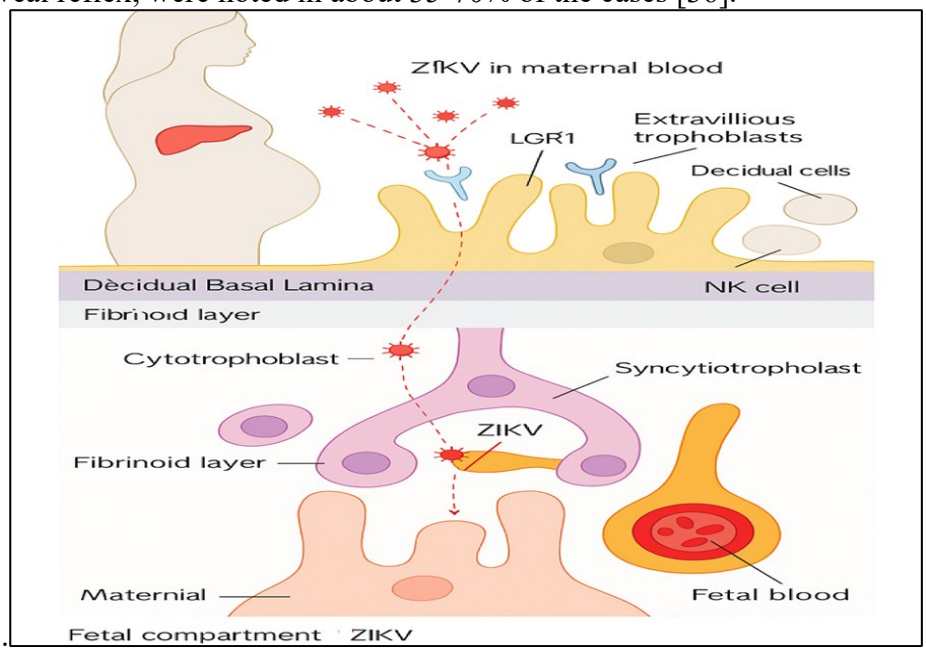

Fig. 5 Illustration showing how Zika virus (ZIKV) crosses the placental barrier.

Experimental studies, some in mouse models, have revealed potential mechanisms (s), by which ZIKV can disturb the development regarding neural progenitor cells, resulting in cortical malformations. Importantly, musculoskeletal, genitourinary and pulmonary abnormalities have been described in CZS infants [16], pointing to phenotypic heterogeneity associated with congenital infection. Despite such results, the molecular and cellular mechanisms associated with vertical transmission remain poorly understood. In vitro experiments show that human and murine blastocysts (particularly the trophectoderm, which is a precursor of placental trophoblasts) are susceptible to ZIKV. The infections may disrupt the development of trophoblast stem cells by inducing apoptosis and necrosis, which could eventually result in early embryonic stasis and contribute to unfavorable fetal outcomes. However, in vivo demonstration of blastocyst infection and consequent embryonal abnormality remained lacking [37]. Susceptibility seems to be dependent on the gestational timing, perhaps related to a maturation of placental defenses over time. A few pathways of transmission have been suggested, including transcellular spread between trophoblast cells, paracellular migration through amniochorionic membrane, autophagy-dependent trafficking and Hofbauer cell (HBC)-mediated spread as well as an antibody-dependent enhancement. These pathways mirror the complex biological determinants of ZIKV placental invasion [38].

While candidate receptors, such as Axl, Tyro3 and Mertk, have been suggested to contribute to ZIKV tropism in other tissue sites, their contribution to transplacental infection is unresolved and hinders our understanding of why the placenta appears selectively infected with ZIKV. Although the neurodevelopmental teratogenic effects of ZIKV have been widely studied, placental pathology is less well explored. Yet, maternal infection with ZIKV is often associated with marked placental abnormalities, including villous damage and vascular impairment that may have their own effects on

fetal brain development. In fact, placental insufficiency alone can generate a clinical phenotype similar to CZS.

In addition to structural birth defects, concern has increased about the developmental health in infants parentally exposed to ZIKV, yet born with no overt abnormality [39]. Follow-up studies have reported: postnatal development of microcephaly, poor cranial growth, impaired motor and speech function. Supporting animal research has also shown that transient maternal ZIKV infection is capable of impairing postnatal growth and cognitive function, even in the absence of morphological abnormalities at birth. Collectively, these results illustrate the complex pathogenicity of ZIKV. Further mechanistic investigations are critical to dissecting the entire vertical transmission range, placental susceptibility and developmentally derived vulnerability after exposure to congenital ZIKV [40].

2.5 SARS-CoV-2 and Pregnancy

Coronaviruses are a group of positive-strand, single-stranded RNA viruses that belong to the Coronaviridae family. It contains SARS-CoV, MERS-CoV and SARS-CoV-2, which have a serious human-to-human transmission ability and toxicity. Coronavirus disease 2019 (COVID-19), caused by the pathogen SARS-CoV-2, is of global public health concern. Clinically, COVID-19 presents along a spectrum from asymptomatic and mild respiratory illness with symptoms like cough, fever and malaise to severe sequelae such as viral pneumonia and acute respiratory distress syndrome (ARDS), often leading to multi-organ failure, commonly underpinning most COVID-19-related cases of mortality [33].

With increasing SARS-CoV-2 prevalence amongst pregnant women, a more nuanced understanding is developing about the effects of this virus on the health of mother and fetus. Early data indicated a higher hospitalization rate in cases of pregnant women (31.50%) compared to non-pregnant ones (5.80%); however, it is unknown whether this was due to increased clinical severity or increased prevention monitoring. The majority of those pregnant patients infected with the disease are mild to moderate symptoms, though there have been a few maternal deaths. Some systematic reviews as well indicate a reduced risk of symptoms (i.e., cough, sore throat, and fatigue) in pregnant women compared to the population at large. However, risk factors such as advanced maternal age, existing morbidities (e.g., obesity, diabetes and hypertension) and social inequities that could raise the chance for adverse maternal health outcomes may still prevail [22].

Maternal respiratory infections have long been associated with unfavorable neonatal outcomes. In the COVID-19 context, an increased incidence of iatrogenic preterm births has been documented, often related to heightened use of cesarean delivery as a precautionary measure. Although select cases of intrauterine growth restriction (IUGR), preterm labor, and neonatal death have been observed, overall rates of stillbirth (<2.5%) and neonatal mortality (<0.6%) remain within the range reported for the general obstetric population [18]. A growing body of research has explored SARS-CoV-2-associated placental pathology. Typical histological observations in placentas from infected pregnancies encompass perivillous fibrin deposition, maternal and intervillous thrombi, foetal vascular malperfusion, infarctions, and chronic inflammatory alterations. However, it remains unclear whether these abnormalities reflect direct viral invasion or secondary effects of systemic maternal illness.

The potential of vertical transmission is one of the main questions that have been raised in relation to pregnancy and SARS-CoV-2 infection and was explored in detail. Reverse transcription polymerase chain reaction (RT-PCR), in situ hybridization, immunohistochemistry, and electron microscopy have all shown the presence of viral components within the placental tissues of several gestational ages [41]. For example, infection localized to syncytiotrophoblasts has been documented in the setting of severe maternal illness. The molecular mechanism of SARS-CoV-2, which enters

host cells via the ACE2 receptor and TMPRSS2 protease, both of which display heterogeneous expression across placental cell populations. Single-cell transcriptomic data suggest that the placenta may be permissive to viral entry, especially when maternal viremia is present.

However, definitive evidence for intra-uterine fetal infection is still lacking. At the beginning of the pandemic, identification of SARS-CoV-2-specific immunoglobulin M (IgM) in neonatal blood and increased levels of IgG and proinflammatory cytokines were also interpreted as indicative for vertical transmission. Later studies have, however, questioned these findings by revealing the limitations associated with using IgM for the diagnosis of congenital infection because of its inconsistent sensitivity and specificity [42]. Strict verification for vertical transmission requires that viral RNA be obtained from a sterile intrauterine specimen or neonatal tissue as close to birth as possible. This entails extensive sampling collecting— placenta, amniotic fluid, cord blood, maternal serum, and neonatal swabs—under strict aseptic circumstances. As yet, no research has convincingly isolated viable virus particles from fetal tissues or sterile compartments and the occurrence of proven transplacental SARS-CoV-2 transmission is currently extremely rare if indeed it occurs at all [43].

Finally, whilst SARS-CoV-2 could cause placental pathology and presence of the virus in placentae, it is not yet convincing that there is direct fetal intrauterine infection. Additional investigations, including standard diagnostic criteria and methodologically robust techniques, are required to understand the possibility of and repercussions from vertical transmission of SARS-CoV-2 during pregnancy [44].

2.6. Emerging Viruses and Pregnancy-Related Complications

Emerging pathogens, including Ebola virus, Rift Valley fever virus (RVFV), and West Nile virus (WNV) are new rising challenges to maternal and fetal health, although the underlying mechanisms of action have often been underestimated. RVFV (an arbovirus) has been linked to fetal loss and stillbirths in infected livestock—a finding that has also been observed in some pregnant women [45]. Experimental ex vivo work has shown that RVFV is able to infect both cytotrophoblasts (CTBs) and syncytiotrophoblasts (STBs), indicating the potential for vertical transmission. Third-trimester human case verified maternal-fetal transition even though the specific transplacental pathway is undefined [46]. WNV has also been associated with vertical transmission and the incidence of neural malformations in neonates that mimic ZIKV-mediated disease. Human placental extravillous trophoblasts (EVTs) are permissive to WNV, consistent with a likely mechanism for fetal spread. In total, gestational infections with these emerging viruses pose significant challenges and deserve increased research focus [40].

3. Mechanisms of Vertical Transmission

Despite growing knowledge, the pathophysiology of viral infections in pregnancy is not well defined, especially regarding vertical transmission. Although the placenta is generally considered a physical barrier against viral infiltration, cellular and molecular mechanisms underpinning such defense are poorly understood [41]. Models from human and murine studies imply multiple lines of defense, including physical barriers, cellular intrinsic anti-viral defenses, and constitutive release of immune-modulating molecules, is shown in Fig. 6. Research on TORCH pathogens and animal models has provided valuable perspectives toward the understanding of transplacental transmission dynamics. It may be possible to devise new therapeutic options for reducing virus-mediated pregnancy failure if these mechanisms can be defined [45].

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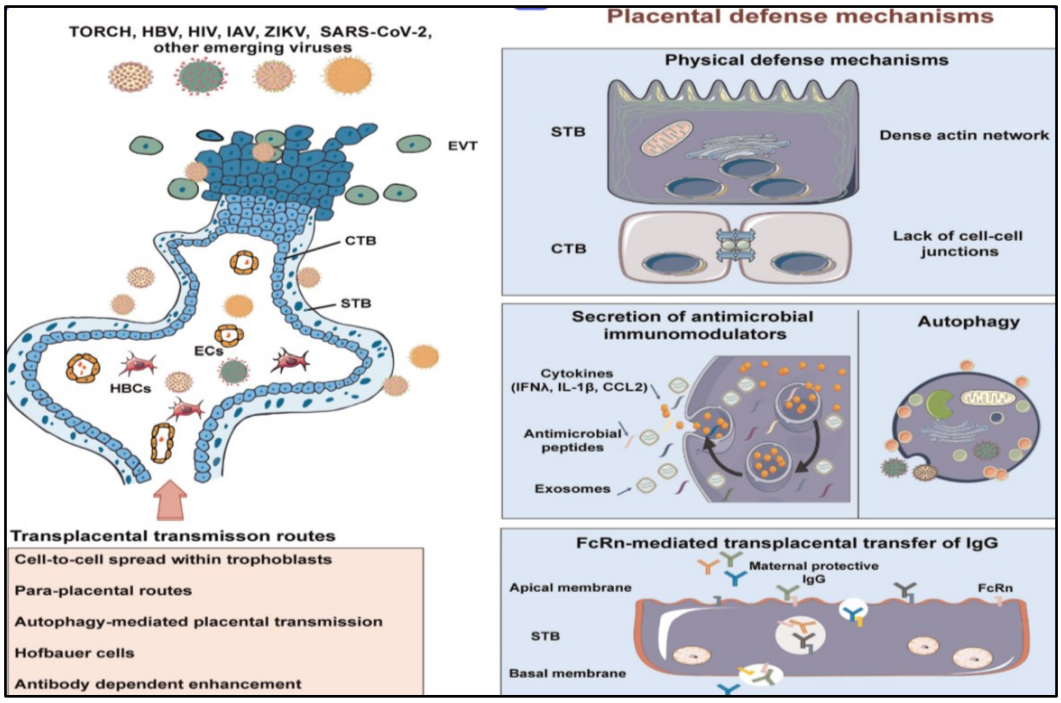

Fig. 6 Placental Antiviral Defence Strategies [44].

Abbreviations: CTB: Cytotrophoblast; EVT: Extravillous trophoblast; ECs: Endothelial cells; HBCs: Hofbauer cells; CCL2: C-C motif chemokine ligand 2; FcRn: Neonatal Fc receptor; IAV: Influenza A virus; IgG: Immunoglobulin G; HBV: Hepatitis B virus; IFN-λ: Interferon lambda; HIV: Human immunodeficiency virus; TORCH: Toxoplasma, Others, Rubella, Cytomegalovirus, and Herpes simplex virus; ZIKV: Zika virus; STB: Syncytiotrophoblast; and SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

4. Effects of Viral Infections on Pregnancy Outcomes

The human placenta consists of floating and anchoring villi. The outer layer of floating villi is a continuous multinucleate syncytiotrophoblast (STB) layer that is in direct contact with maternal blood for the exchange of nutrients, gases and waste products. This layer is also important for endocrine signaling, a prerequisite of pregnancy adaptation. A layer of proliferative mononuclear CTBs, the stem cells that differentiate into STBs through fusion, is found beneath the STBs. Alternatively, a subset of them will differentiate into EVTs to invade the decidua and remodel maternal vasculature. The Extra villous trophoblasts are immune-selective, producing human leukocyte antigen G (HLA-G), which mediates maternal-fetal tolerance [28].

Trophoblast subtypes differ in susceptibility for viral infection. STBs are relatively resistant to several virus pathogens, while Cytotrophoblast and in particular EVTs show greater sensitivity. For instance, cytomegalovirus preferentially targets CTBs as opposed to STBs in placental explant model. However, more recent observations suggest that SARS-CoV-2 may infect primarily STBs because of their expression regarding viral receptors. EVTs have exhibited upregulated susceptibility to infection, and cytomegalovirus DNA in EVTs of term placenta has been seen. ZIKV, based on the first-trimester villous explants models, seems to avoid STBs and target EVTs, probably by utilizing HLA-G expression as a viral sanctuary [41]. Immune cells that are derived from maternal tissue (decidual NK cells, T cell subsets and Hofbauer cells (HBCs), and macrophages) have diverse effects. These functions, involving immune balance and often facilitate viral spread. For example, decidual NK-cells have been shown to suppress HIV in macrophages through contact-dependent killing as well as interferon release. In contrast, HBCs have increased susceptibility to ZIKV and this may help in the spread to the fetal compartment [33].

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5. Diagnosis and Monitoring

It is crucial for the management of maternal and fetal disease risk that viral infections in pregnancy are diagnosed correctly and monitored. Diagnostic protocols differ according to the virus, but are generally based on serological tests, nucleic acid amplification assays (NAAT) and imaging. For instance, HBV screening includes the detection regarding surface antigen HBsAg, e antigen HBeAg as well as identification regarding the viral DNA levels [42]. For HIV-positive pregnancies, maternal viral load and CD4+ T cell counts are monitored to direct antiretroviral therapy and delivery management. For the novel ZIKV and SARS-CoV2, diagnosis may be by RT-PCR of maternal serum, amniotic fluid, or placental tissues.

Nevertheless, to eventually confirm vertical transmission, extensive sampling of sterile intrauterine compartments such as cord blood and neonatal swabs is the prerequisite, following birth. Imaging techniques such as fetal ultrasound and MRI are also used for the identification of structural abnormalities associated with congenital infections [31]. Routine monitoring during pregnancy makes it easier to find problems like placental insufficiency, IUGR, along fetal distress early on. There is high importance in combining the lab tests with clinical surveillance for the purpose of improving the fetal-maternal health, also making early interventions [47].

6. Prevention and Treatment Strategies

Placenta can be defined as one of the multi-layered defenses against viruses, which include structural barriers like syncytiotrophoblast (STB), which has antimicrobial properties, as well as limiting the entry of pathogens. Furthermore, autophagy, which is considered one of the cellular degradation pathways upregulated in term trophoblasts as well as functions as a critical factor inhibiting viral replication, along with vertical transmission. Experimental models demonstrate that blocking autophagy might restrict fetal infection, also in the setting of ZIKV [40]. Aside from physical and cellular barriers, trophoblasts secrete antiviral molecules, including IFNs. Type III IFNs have demonstrated protective capacity in human and animal models and are being evaluated as prophylactic agents.

Moreover, pattern recognition receptors (i.e., TLRs, RIG-I) and placenta-specific microRNA also make some contribution in innate immunity through regulation of cytokine responses and promote autophagy. Although these natural defenses provide intrinsic protection, clinical preventive and treatment measures of viral infections during pregnancy require a combination of screening, vaccination, antiviral therapy and obstetric interventions [35]. As such, universal antenatal screening for viruses such as HBV and HIV is efficient in diagnosis and risk assessment.

For HBV, maternal antiviral therapy with Tenofovir, along with neonatal immune prophylaxis, substantially reduces vertical transmission. In HIV-infected pregnancies, the use of combination antiretroviral therapy (cART), elective cesarean delivery, and avoidance of breastfeeding reduces transmission rates to less than 1%. Vaccination is still the main prevention. Inactivated influenza vaccines are used in pregnancy and have been shown to be both safe and effective in reducing maternal and neonatal complications. [39] Safe vaccines for emerging viruses, like ZIKV and SARS-CoV-2 are still under investigation with mRNA-based platforms showing promise. Gestational age, maternal immunity status and drug teratogenicity should also be taken into account when decided how to treat. Optimizing the trade-off between maternal viral suppression and fetal safety involves personalized treatment and interdisciplinary cooperation. Further investigations are necessary to improve therapeutic protocols, so as to achieve a favorable outcome for mother and child [41].

7. Psychological and Social Aspects

When a pregnant woman comes down with a viral infection, she may experience it in her emotions and mental health. She may be worried about whether her baby is healthy or scared that she'll pass

the virus to the fetus. Some women feel depressed, stressed, or guilty, particularly if the virus is known to cause problems in newborns. Sometimes others around her may treat her differently or avoid her and make her feel alone. Moreover, some infections, such as HIV or COVID-19, may generate fear or misunderstanding within society [44]. And this may contribute to receiving less support from family or friends. This is why it is so important for the doctors and nurses to talk to the pregnant women, help them feel that they are safe, and also provide emotional support during this time [46].

8. Recent Examples

There have been a few viruses in recent years that have posed threats to pregnant women. For instance, amid the COVID-19 pandemic, many pregnant women have been more likely to be at increased risk of preterm delivery or needing surgery for childbirth. Among the newborns, some were smaller than expected. And, of course, there is the Zika virus that spread in Brazil and led to babies being born with small heads and brain problems. Those cases show that getting a virus while pregnant might be dangerous. Also, they remind us that the doctors need to think quickly and act on the test results for the purpose of giving the right care and saving both the mom and the baby [45].

9. Conclusion

Maternal-fetal syndromes that are induced virally arise from complex courses regarding viral virulence, cellular tropism, in addition to immune responses to the placenta. There is high importance in gaining a deeper understanding of how the physiological changes throughout pregnancy influence susceptibility. Learning about how placental immunity works help scientists make vaccines and medicines that are safe for pregnant women to use. For stopping the future epidemics as well as lessening the maternal-fetal morbidity burden from unexpected or known consequences of new viral infections, strong foundational research is necessary.

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