

# Viral Infections During Pregnancy: The Big Challenge Threatening Maternal and Fetal Health

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## Abstract

Viral infections during pregnancy are associated with adverse pregnancy outcomes, including maternal and fetal mortality, pregnancy loss, premature labor, and congenital anomalies. Mammalian gestation encounters an immunological paradox wherein the placenta balances the tolerance of an allogeneic fetus with protection against pathogens. Viruses cannot easily transmit from mother to fetus due to physical and immunological barriers at the maternal-fetal interface posing a restricted threat to the fetus and newborns. Despite this, the unknown strategies utilized by certain viruses could weaken the placental barrier to trigger severe maternal and fetal health issues especially through vertical transmission, which was not fully understood until now. In this review, we summarize diverse aspects of the major viral infections relevant to pregnancy, including the characteristics of pathogenesis, related maternal-fetal complications, and the underlying molecular and cellular mechanisms of vertical transmission. We highlight the fundamental signatures of complex placental defense mechanisms, which will prepare us to fight the next emerging and re-emerging infectious disease in the pregnancy population.

**Keywords:** Trophoblasts; Congenital infection; Hepatitis B virus; Human immunodeficiency virus; Influenza A virus; Severe acute respiratory syndrome coronavirus 2; Zika virus

## Introduction

The recent outbreaks of emerging viruses, like Zika virus (ZIKV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), repeatedly raise concerns about the impacts of viral infections during pregnancy on maternal and fetal health.<sup>1,2</sup> In general, a series of physiological adaptations to pregnancy, especially immunological and endocrinological changes, make the mother and fetus more susceptible to certain viral and bacterial infections, which is associated with greater risk for severe complications caused by infectious diseases.<sup>3</sup> The poor outcomes triggered by viral infections during pregnancy include maternal morbidity, pregnancy loss, stillbirth, intrauterine growth restriction (IUGR), preterm birth, neonatal death, and congenital abnormalities.<sup>3,4</sup> However, given the potential safety and toxicity issues regarding the usage of antiviral treatments and vaccines during pregnancy, pregnant women are believed to be even more vulnerable to devastating consequences induced by viral infections.<sup>5</sup>

The human placenta, a specialized and complex organ that is formed exclusively during pregnancy, is indispensable for sustaining fetal growth and development normally.<sup>6</sup> The placenta presents an immunological paradox since it simultaneously bears the responsibility of immunologic tolerance to the fetus and retaining immunity against potential infections. Without complicated pathogen defense strategies at the maternal-fetal surface, fetal survival and development cannot be preserved due to the constant onslaught of microorganisms in our environment. However, several underappreciated mechanisms could be utilized by selective pathogens to escape from the monitoring of placenta resulting in maternal-fetal transmission. The pathogenesis of typical TORCH pathogens (refers to Toxoplasma, Others, Rubella, Cytomegalovirus, and Herpes simplex virus) causing vertical transmission has been reviewed in detail elsewhere.<sup>3,7,8</sup> In this review, we mainly focus on the classic and emerging virus causing desperate maternal-fetal outcomes, including the hepatitis B virus (HBV), human immunodeficiency virus (HIV), influenza A virus (IAV), ZIKV, and SARS-CoV-2. We discuss the basic biology of viral infections during pregnancy, their pathogenesis characteristics, maternal-fetal complications they cause (Fig. 1), and the underlying molecular and cellular mechanisms of vertical transmission from the evidence available to date. Moreover, we elaborate a concise description of placental defense mechanisms in response to viral insults for a better understanding of strategies utilized to restrict the maternal-fetal transmission of pathogens, which could be also targeted as potential antiviral therapies.

## Viral infections during pregnancy

### HBV

HBV, a member of the *Hepadnaviridae* family, is the most common blood-borne pathogen globally, which could lead to acute and chronic hepatitis in humans. The transmission routes of HBV are predominantly through blood and

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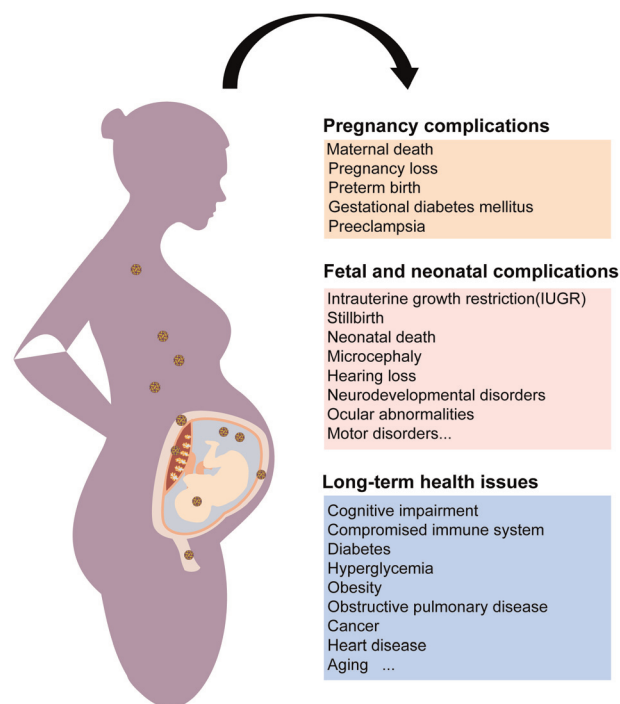
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**Figure 1.** Viral infections during pregnancy and the corresponding maternal-fetal outcomes. Viral infections throughout the entire course of pregnancy can lead to diverse pregnancy complications such as maternal death, pregnancy loss, and preterm birth. Fetal and neonatal anomalies relevant to viral infections during pregnancy, especially the ones causing vertical transmission, can cause IUGR, stillbirth, microcephaly, motor disorders, and other neurodevelopmental disorders. Additionally, the offspring with prenatal exposure to maternal infectious diseases also encounter lifelong health issues.

bodily fluids, vertical transmission, as well as sexual and parenteral contacts.<sup>9</sup> Perinatal transmission from the mother to fetus or newborns is still responsible for the most chronic HBV infections in adults who are more prone to severe liver diseases and poor responses to antiviral therapies.<sup>10,11</sup> The risk of perinatal transmission in case of mothers with positive HBV e antigen or high viral loads has been estimated to be as high as 90% if the newborns accept no immunoprophylaxis treatment (includes HBV vaccine and immune globulin).<sup>12</sup> Therefore, to prevent the vertical transmission of HBV in advance, universal maternal screenings for the HBV surface antigen, HBV e antigen, viral load, and alanine aminotransferase level during pregnancy are priorities to be adopted.<sup>12</sup> Although immunoprophylaxis at birth together with antiviral treatments for mothers in endemic areas currently are the common and effective strategies for global elimination and preventive interventions of HBV, vertical transmission of HBV occurs with high prevalence and should be taken seriously due to uneven coverage of vaccine globally and/or prophylaxis failure.<sup>13–15</sup>

Although pregnancy complications related to HBV infection if any are minimal, clinical evidence has indicated that chronic HBV infection may be vaguely associated with gestational diabetes, preterm labor, antepartum hemorrhage, and preeclampsia.<sup>16–18</sup> For preterm birth, several meta-analyses have confirmed that seropositivity for HBV surface antigen in pregnant women could increase

the risk of preterm labor, while another study involving 6781 prematurity cases inconsistently revealed no association with HBV infection in the preterm birth group.<sup>17,19–22</sup> Worthy of note, in the above-mentioned studies, half of the enrolled pregnant women exhibited abnormal liver functions such as non-alcoholic fatty liver disease, which may be an independent risk factor for preterm labor rather than the virus per se. Interestingly, women with HBV infection were observed to develop 2.18-fold higher antepartum hemorrhage, probably due to placenta previa and placental abruption, which is attributed to coinfection of HBV with other viruses.<sup>21</sup> Unexpectedly, a negative association or protective effect of HBV infection on preeclampsia was demonstrated in a meta-analysis involving 11,566 cases.<sup>23</sup> Nonetheless, the explicit causes underlying the above adverse pregnancy outcomes have not been extensively evaluated until now, placental inflammation, insulin resistance, increased immunotolerance, or impaired immune response upon HBV infection were proposed as suspected mechanisms.<sup>18,24</sup>

Furthermore, the hint of fetal and neonatal anomalies was also observed in pregnant women with chronic infection. It was noticed that 60% increased non-reassuring fetal heart rate patterns and 80% increase in asphyxia referring to 7600 pregnant HBV carriers from 18 studies by meta-analysis suggested fetal distress conditions related to HBV infection.<sup>25,26</sup> Additionally, 25.8% increased low birth weight and small infants were reported to be associated with HBV infection, while abnormally enhanced fetal growth and macrosomia were also found in a series of researches.<sup>26–28</sup> Viral genotypes, co-existing hepatic disorders, coinfections with other pathogenic organisms, synergism with pregnancy complications, and the phase of chronic HBV infection probably led to contradictory phenotypes of fetal growth.<sup>29,30</sup>

The path of HBV vertical transmission includes intrauterine transmission, labor, and delivery, as well as breastfeeding. The primary risk period for infant HBV infection is the peripartum period. Most cases of infection occur during delivery when the mucosa of newborns is easily contaminated by maternal blood and secretions that contain high viral loads. Alternatively, some researchers suggested that different placental compartments from the maternal side to the fetal side, such as trophoblasts and endothelial cells of villous vessels, can be infected by HBV, indicating a potential mechanism of HBV transplacental infection.<sup>31,32</sup> Moreover, clinical studies have shown that mother-to-child transmission of HBV can be almost completely blocked by maternal antiviral therapy during pregnancy, supporting the plausibility of intrauterine infection.<sup>33,34</sup> However, the presence of intrauterine HBV transmission is still debatable as shown by some controversial evidence.<sup>35</sup> Therefore, the possibility and mechanisms underpinning HBV intrauterine transmission require more comprehensive in-depth clinical and basic research, which would help clinicians to improve prophylactic measures preventing mother-to-child transmission of HBV.<sup>36</sup> At present, exploring the reasons of prophylaxis failure will be one of the big challenges in clinical practice to successfully eliminate HBV vertical transmission. Meanwhile, a comprehensive long-term safety profile of antiviral prophylaxis also needs to be assessed in the future.<sup>37,38</sup>

## HIV

HIV (including two types HIV-1 and HIV-2) destroys the immune system and eventually causes acquired immunodeficiency syndrome.<sup>39</sup> HIV-1 has stronger transmission capabilities and pathogenicity than HIV-2, herein we discuss HIV-1 primarily.<sup>40</sup> Since the beginning of this century, >1.5 million childbearing age women have been annually threatened by HIV-1 infection to varying extents.<sup>41</sup> Maternal HIV-1 infection accounts for adverse pregnancy outcomes, such as premature labor, miscarriage, and IUGR, which deteriorates in women with advanced HIV disease or immunosuppression.<sup>41–43</sup> The vertical transmission of HIV could be archived through intrauterine, intrapartum (contacting with mother's blood, cervix, and vaginal secretions), and postpartum transmission. Maternal viral load, immune and nutritional status, and fetal birth mode will directly affect the likelihood and efficiency of HIV-1 perinatal transmission. Fortunately, the risk of HIV-1 vertical transmission could be decreased from 40% to <1% if the appropriate clinical management including cesarean section, combination antiretroviral therapy (cART), neonatal antiretroviral administration, and bottle-feeding were implemented in HIV-1-infected mothers during pregnancy.<sup>44–47</sup>

The definitive mechanisms of HIV vertical transmission remain largely unknown, especially the ones contributing to intrauterine transmission. Despite a large number of in utero transmission cases being documented in the third trimester, detectable HIV in aborted fetuses as early as 8 weeks implicates that HIV could disseminate to the fetus prior to a mature placental barrier.<sup>48</sup> It has been originally suggested that HIV-1 circulating in the amniotic cavity could pass through the mucosal surface of fetal oropharynx or gastrointestinal tract, while recently published studies have not observed HIV-1 in the amniotic fluid even if systemic viral titers of some participants in plasma exceeded  $10^5$  copies/mL.<sup>49–51</sup> Additionally, fetal HIV infection in utero is hypothesized primarily to occur by the transplacental route, which is supported by the presence of HIV-1 in placentas from infected mothers.<sup>52</sup> Although HIV could infect trophoblasts straight by a syncytin-dependent mechanism, the virus enters the trophoblasts with much lower efficacy compared to CD4+ cells.<sup>53–55</sup> Several in vivo studies have also confirmed that HIV-1 resides within placental Hofbauer cells (HBCs).<sup>56,57</sup> Indeed, these unique macrophages express the HIV-1 (co)-receptors such as CD4, C-X-C motif chemokine receptor 4, and DC-SIGN, along with fragment crystallizable (Fc)  $\gamma$  receptors which may sequester HIV-1-antibody (Ab) immune complexes for in utero transmission of HIV-1.<sup>58</sup> Therefore, transcytosis transmission of Ab-associated virions is another hypothesis of HIV vertical transmission.

It is not clear how HIV infection causes specific adverse pregnancy outcomes. Therein, recognizing the alternations of placental structural and functional features upon HIV infection could provide mechanistic insights into fetal and neonatal health. Gross pathological assessments of placental specimens have identified low placental weight, maternal vascular malperfusion, chorioamnionitis, and placental inflammation relative to HIV infection.<sup>59,60</sup> More recently, Kalk *et al.*<sup>61</sup> reported HIV-infection induced a 2.21-fold higher frequency of maternal vascular malperfusion, which

can significantly boost the risk of IUGR and fetal demise. Crucially, excessive inflammatory response, disordered immune cell composition, and performance in HIV-1 infected placenta could also directly affect the fetal growth and development leading to babies with low birth weight. For instance, several observations have shown that the functions and subsets of tissue-resident T cells were changed, specifically a growing tendency of activated tumor necrosis factor- $\alpha$ -producing T cells in HIV-1-infected pregnant women.<sup>62</sup> Besides T cells, other studies have shown that HIV-1 infection could impair natural killer (NK) cell effector functions and reduce anergic NK cells accumulation, which may cause the insufficient formation of placental vasculatures and nutrient supply for the infant, thereupon then, fetal growth is impacted.<sup>63</sup>

Vertical transmission of HIV has been effectively reduced in the last two decades mainly attributing to the highly active antiretroviral therapy. The anti-HIV interventions include strategies either reducing maternal viral exposure and load or prophylaxis in the infants by antiretroviral treatment. The pharmacological nature of antiretroviral reagents covers the antagonists of viral enzymes such as reverse transcriptase, protease, and integrase, as well as HIV co-receptor inhibitors.<sup>63,64</sup> However, cART could simultaneously increase the risk of pregnancy complications, particularly preterm birth.<sup>65</sup> A study from Europe first reported the association of cART and preterm birth in 1998, with subsequent studies complementing this phenomenon and speculating on the possible mechanisms: (1) Certain antiviral medicine, Ritonavir for example, may directly reduce progesterone and estradiol levels and consequently lead to IUGR, which provides a potential mechanistic link between protease inhibitors-based antiviral treatment and greater risk of preterm birth.<sup>66</sup> (2) Antiretroviral agents could cross the blood-placenta barrier to varying degrees, thus the toxicity of specific drugs in adults could be observed theoretically in the exposed fetuses and newborns as well.<sup>67</sup> Moreover, fetuses may be more sensitive than adults to certain toxic antiviral medicines, such as zidovudine and stavudine, leading to mitochondrial dysfunction and inflammasome activation in placentas. (3) Usage of cART may dysregulate immune response systemically and locally at the maternal-fetal interface, which could cause a shifted immunological feature during pregnancy to favor preterm birth.<sup>68</sup> Overall, assessing the potential health threats of such antiretrovirals exposures are quite challenging but critical for optimizing the cART treatment on HIV-1-infected pregnant women.

## IAV

Influenza viruses could cause acute respiratory symptoms including fever, malaise, and coughing. Although influenza viruses are classified into A, B, C, and D types, only type A viruses, such as swine influenza (H1N1), are recognized to have a wide range of hosts including mankind and become a major driver of human infectious diseases.<sup>69</sup> Airborne droplets are the main route of IAV transmission from human to human, potentially, active virus particles can also spread to the eyes or nose via contacting with other body fluids and contaminated inanimate objects.<sup>69</sup> The current epidemiological data show that the symptoms of

H1N1 infection in the general population are mild and self-healing, while people with chronic diseases and from the age group of >60 years hold the highest mortality rate, indicating that IAV poses a greater threat to high-risk groups.<sup>70,71</sup> Pregnant women have been found 4~5 times more susceptible to IAV infections and increased risk for extrapulmonary complications than nonpregnant women.<sup>72,73</sup> During the 2009 pandemic of IAV, pregnant women were more frequently hospitalized than individuals in the general population.<sup>74</sup> In addition, the maternal mortality rate of IAV infection was significantly higher in the United States, which is in line with 27%–45% maternal mortality and 52% pregnancy loss rate during the 1918 pandemic.<sup>75</sup> It should be noted that the possibility of adverse maternal outcomes increases with the advancing gestational age.<sup>75</sup> Women with full-term pregnancy are five times more likely to be hospitalized with IAV infection than the ones at postpartum or early pregnancy stage.<sup>76</sup> Reviewing the characteristics of patients in the past influenza epidemic, it was found that the proportion of hospitalized pregnant women with heart and lung damages increased significantly in the later trimester comparing early-to-middle trimester.<sup>74</sup> Furthermore, pregnant women who are complicated with obesity, metabolic diseases, smoking history, and heart and respiratory diseases should be given extra attention to avoid severe or even life-threatening symptoms.<sup>77,78</sup>

Thus far, mechanisms underlying the high occurrence and severity of IAV infection have not been fully clarified. Pregnant women are particularly vulnerable to IAV infection, which may partially result from pregnancy-induced immunological changes, including suppressed cell-mediated immunity, alterations in NK cell activity, by contrast, enhanced humoral immunity.<sup>79–81</sup> For example, several studies have suggested the significantly attenuated interferon (IFN) response in peripheral mononuclear cells isolated from pregnant women with IAV infection, indicating a possible mechanism underlying increased susceptibility to viral infections during pregnancy.<sup>82</sup> Furthermore, others suggested that inactivated lung dendritic cells and virus-specific CD8 T cells deficiency in the airway contributed to the inability to control the virus in pregnancy.<sup>83,84</sup> Besides, anatomical and physiological changes of a pregnant woman could also contribute to the high-risk adverse pregnancy outcomes in the setting of IAV infection.<sup>85</sup> Functional changes of the cardiopulmonary system during pregnancy, critical for meeting the metabolic demands of the mother and fetus, have been recognized as a risk factor for severe influenza infection. During pregnancy, increased maternal oxygen consumption and lung tidal volumes, with reduced residual volume, expiratory reserve volume, and functional residual capacity, could compromise the compensatory capacity of the respiratory system to meet the IAV challenge and result in worse outcomes.<sup>86,87</sup>

IAV infection during pregnancy causes severe fetal and neonatal complications as well, including IUGR, preterm birth, neonatal death, and neurological disorders. The reasons for fetal mortality and morbidity upon IAV infection during pregnancy are currently unclear. Different from TORCH pathogens, vertical transmission of IAV appears to be rare because of infrequent viremia, despite a recent study reported that the highly pathogenic strain

H5N1 could be detected in the placental trophoblasts and fetal respiratory tract.<sup>88,89</sup> Maternal symptoms of IAV infection, such as fever, hypoxia, and septic shock, could exert influence on fetal health in the absence of direct fetal infection. Recently, Liong *et al.*<sup>90</sup> demonstrated virus dissemination to major maternal blood vessels leads to a peripheral “vascular storm”, featured as profoundly elevated proinflammatory and antiviral mediators in the maternal vascular system, which could subsequently induce hypoxia in the placenta and fetal brain. Moreover, accumulating evidence suggests that offspring born to prenatally IAV-infected mothers exposed high risk of chronic diseases in later life, among which neurocognitive disorders, autism for instance, are the best described ones.<sup>91–93</sup> Animal models corroborate this link and suggest that IAV infection can affect lifelong neuropathology and altered behaviors in offspring, which may be due to oxygen deprivation, placental transmission of cytokines, and antibodies or dysregulated hormone signaling after infection with influenza virus.<sup>94,95</sup> Moreover, Jacobsen *et al.*<sup>92</sup> proposed that neonates from IAV-infected pregnant dame exhibited increased susceptibility to viral and bacterial infections due to reduced hematopoietic development and immune responses, which further highlights the importance of fundamental mechanistic study regarding IAV induced poor maternal-fetal outcomes in the future.

## ZIKV

ZIKV is a single-stranded RNA virus of the *Flaviviridae* family, which was originally isolated from a rhesus monkey residing in Uganda. It spread globally from 2015 to 2016 and led to a Public Health Emergency of International Concern declared by the World Health Organization due to emerging neuropathogenicity such as the Guillain-Barré syndrome in adults and microcephaly in neonates, respectively.<sup>96</sup> Although ZIKV is initially recognized as a mosquito-borne virus predominately transmitted by *Aedes*, there has been a great accumulation of new evidence that ZIKV can be transmitted in many new routes, especially through sexual contact, blood transfusion, and most important of all, vertical transmission. About 80% of ZIKV infection cases in the general population are asymptomatic like other arbovirus infections, and only a few patients develop symptoms such as fever, joint pain, and malaise. It is estimated that the mortality rate of ZIKV infection is as low as 0.01%, while a limited number of death cases occurred in individuals with immunocompromised complications.<sup>2</sup> The clinical manifestations of systemic ZIKV infections during pregnancy present similar symptoms like those described in nonpregnant individuals, usually mild and self-limiting diseases, suggesting no specific maternal clinical features and increased pathogenicity in general. Nevertheless, clinical and basic investigations have shown that congenital ZIKV infection could dramatically provoke pregnancy diseases, such as miscarriage, IUGR, premature delivery, and fetal death.<sup>97,98</sup>

Moreover, the fetal congenital Zika syndrome (CZS), a unique pattern of birth defects and disabilities found among fetuses and babies born to mothers exposed to ZIKV during pregnancy, has attracted extensive attention since the most recent epidemics in the Americas.<sup>99</sup> Until

now, >4000 infants worldwide have laboratory-confirmed CZS.<sup>96,100</sup> Typical clinical manifestations of CZS mainly include severe microcephaly, severe brain abnormalities (subcortical calcifications, ventriculomegaly), ocular abnormalities, etc.<sup>101</sup> A study of Brazilian infants with microcephaly caused by ZIKV infection revealed that 93% of infants had brain calcification, 69% encountered cortical developmental malformations such as lissencephaly and pachygyria, and 66% developed ventriculomegaly due to brain atrophy.<sup>102</sup> Following studies have demonstrated that 35%–70% of infants with microcephaly and cerebral calcification are accompanied by a spectrum of ocular alterations such as optic nerve hypoplasia and double-ring sign, foveal reflex loss, chorioretinal macular atrophy, and cataracts.<sup>101,103,104</sup> Mechanistically, Li *et al.*<sup>105</sup> reported a direct link between ZIKV infection in the embryonic brain and microcephaly by disrupting neural progenitor development in a mouse model, which could provide valuable resources for further exploration of the underlying mechanisms and management of ZIKV-related pathological effects. Besides the above disorders, musculoskeletal, genitourinary, and pulmonary abnormalities are also observed in CZS babies, indicating phenotypic diversity caused by congenital ZIKV infection.<sup>106–108</sup>

Sadly, up to now, very little is understood about the pathogenic mechanisms underlying the vertical transmission of ZIKV. It has been reported that ZIKV can infect human and mouse blastocysts *in vitro*, especially in trophoblast which gives rise to various trophoblast lineages in the mature placenta. This result indicates that ZIKV infection may directly lead to the developmental restriction of blastocysts and trophoblast stem cells through apoptosis and necrosis pathway, and eventually cause the occurrence of severe CZS.<sup>109</sup> However, whether ZIKV could infect blastocysts and induce any embryonic abnormality *in vivo* remains unknown. If it is true, it could explain at least partially why ZIKV infection in early pregnancy causes more serious adverse pregnancy outcomes observed in human and mouse models.<sup>106,110,111</sup> Another explanation for different vulnerabilities to ZIKV infection at different pregnancy stages is due to the gradually gained placental defense mechanisms along with the progress of pregnancy, which will be discussed in detail below. In addition, the transplacental transmission routines of ZIKV are still debatable. Several cellular mechanisms may mediate the vertical transmission of ZIKV, including cell-to-cell spread within trophoblasts, para-placental routes (traversing the amino-chorion), autophagy-mediated placental transmission, ZIKV dissemination seeded from infected HBCs, and Ab dependent enhancement of ZIKV infection.<sup>112,113</sup> Each of those mechanisms is unique somehow, indicating the complexity and heterogeneity of vertical transmitted ZIKV infection, which need to be further explored in future in-depth mechanistic studies. It is worthy of note that although some molecules are proposed as potential receptors or host factors for ZIKV infections in different organs, such as Axl, Tyro3, and Mertk, none of them has been validated in the setting of transplacental infection, which impedes the mechanisms underpinning strong placental tropism of ZIKV.<sup>114,115</sup>

Extensive researches have focused on how ZIKV infection targeting the developing brain independently

causes neurological damages in fetuses. Nonetheless, maternal ZIKV infection in human and multiple animal models resulting in microcephaly was accompanied by substantial placental insufficiency and abnormalities, where few studies keep a watchful eye on how placental structure and function are modified upon ZIKV infection and the contribution of placental defects to CZS.<sup>116,117</sup> In fact, malfunction of placenta alone could induce CZS-like diseases. Thus, whether CZS is caused by direct ZIKV infection or placental insufficiency indirectly (or combined effects) is another aspect worth pondering. Moreover, whether ZIKV infection during pregnancy could affect neonatal development and even long-term health issues especially in those who had no obvious CZS at birth? There is evidence that some normal-appearing newborns born to the mother with ZIKV exposure during pregnancy developed a microcephaly phenotype during postnatal development, such as head growth restrictions and brain neuroimaging abnormalities. Furthermore, motor disorders and neurodevelopmental delay in the language function in infants can also be observed after birth in some ZIKV-exposed cases *in utero*.<sup>118</sup> In line with those, Paul *et al.*<sup>119</sup> did not observe significant morphological alterations and ZIKV existence in perinatal mice after intraperitoneal ZIKV infection on pregnant dams, while manifested postnatal growth impediments and neuro-behavioral deficits appeared later in postnatal life. Therefore, a transient ZIKV infection during pregnancy is likely to affect future development and health of the neonates and even adulthood health in a long run, which still needs in-depth mechanistic studies to address.

### SARS-CoV-2

Coronaviruses belonging to the family *Coronaviridae* are positive-sense RNA viruses.<sup>120</sup> To date, the Middle East respiratory syndrome coronavirus, SARS-CoV, and SARS-CoV-2 are deadly pathogens with high transmissibility.<sup>120</sup> The outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 seriously threatens the health of people all over the world.<sup>121</sup> Clinical manifestations of COVID-19 range from asymptomatic, through mildly symptomatic with cough, fever, myalgia, and malaise to full-blown viral pneumonia.<sup>121</sup> Acute respiratory distress syndrome belonging to serious COVID-19 can progress to multi-organ failure that figured the main cause of death worldwide in infected patients.<sup>121</sup> As new evidence accumulated exponentially due to the increasing number of infected pregnant women, a picture of how COVID-19 impacts pregnant women and their infants has been crystallized.<sup>122–125</sup>

At the beginning of the current SARS-CoV-2 epidemic, a substantially higher hospitalization percentages in pregnant women (31.5%) than non-pregnant women (5.8%) were reported based on the limited cases.<sup>126,127</sup> However, whether the higher hospitalization rate is due to special cautions given to the pregnant population rather than more serious COVID-19 is still controversial.<sup>127,128</sup> In addition, a few maternal death cases were reported in pregnant women infected with SARS-CoV-2, while most pregnant women positive for SARS-CoV-2 showed overall only mild to moderate symptoms of COVID-19.<sup>129–134</sup> On the contrary, a systematic review discovered that pregnant

women even have a lower incidence of cough, sore throat, fatigue, headache, and diarrhea. Notably, risk factors such as race, nutritional status, age, and chronic diseases including obesity, diabetes, and hypertension could aggravate COVID-19 related poor outcomes.<sup>127,135–137</sup>

In general, viral infections on the maternal respiratory track were associated with higher rates of several adverse fetal-neonatal consequences, including IUGR, preterm birth, in some serious cases, even intrauterine fetal demise and neonatal death.<sup>74,137–141</sup> Thus far, most larger cohort studies surely confirmed the intense relationship between COVID-19 during pregnancy and iatrogenic preterm birth.<sup>142–144</sup> Interestingly, the increased preterm labor may be related to a higher rate of cesarean delivery, which might be the optimal scheme to ensure the safety of both mother and fetus under the scenario of SARS-CoV-2 infection.<sup>145,146</sup> Fortunately, although certain neonatal abnormalities were observed, the overall frequency of adverse outcomes in the neonates from women with COVID-19 showed no significant difference in general.<sup>145</sup> Systematic reviews reported that the rates of stillbirth and neonatal death in pregnancy with COVID-19 were <2.5% and 0.6%,<sup>147,148</sup> respectively, which is comparable with healthy pregnant women. Despite this, SARS-CoV-2 was proven to cross the blood-brain barrier, proposing the possibility that it could attack brain tissues leading to the potential pathogenesis of neural tube defects.<sup>149</sup> Given the importance of placenta throughout the entire episodes of pregnancy, information on pathological changes of placentas from mothers with COVID-19 is rapidly increasing. The most common pathological signature of SARS-CoV-2 infected placentas includes perivillous fibrin diffusion, maternal and fetal vascular malperfusion, intervillous thrombi, multi-focal infarctions, and chronic inflammatory lesions.<sup>1,150</sup> However, whether the pathological changes of placenta are directly caused by the viral infection at the maternal-fetal interface or secondary to systemic infection needs further confirmation.

A significant concern regarding COVID-19 during pregnancy is whether vertical transmission of SARS-CoV-2 exists and what are the corresponding impacts on fetal-neonatal outcomes. Recent investigations demonstrated the presence of SARS-CoV-2 in infected placentas at different gestation stages through reverse transcriptase polymerase chain reaction, RNA in situ hybridization, immunohistochemistry, and electron microscopy, which suggested potential transplacental infection caused by the SARS-CoV-2.<sup>151–156</sup> For example, Hosier *et al.*<sup>151</sup> found that the placenta from a pregnant woman with symptomatic COVID-19 infection at the second trimester complicated by severe preeclampsia showed SARS-CoV-2 infection localized predominantly to syncytiotrophoblasts (STBs). Mechanistically, the transplacental transmission of SARS-CoV-2 is also implicated by extrapolating placental transcriptomics. The molecular basis of SARS-CoV-2 infection is highly dependent on the angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2).<sup>123</sup> Blockade of ACE2 or TMPRSS2 protein function can significantly reduce the sensitivity of cells to the virus, suggesting their expression dynamics may be responsible for SARS-CoV-2 infectivity, tropism, and pathogenicity.<sup>123,157,158</sup> Single-cell RNA sequencing on maternal-fetal interface revealed the heterogenous expres-

sion patterns of ACE2 and TMPRSS2 in different cell types, which suggests that placentas might be vulnerable to SARS-CoV-2 floating in the maternal blood and seed the dissemination of the virus to fetus.<sup>159–161</sup>

Although the presence of virus in placental cells raises the possibility of transplacental transmission of SARS-CoV-2, the evidence supporting intrauterine fetal infection is controversial. Original studies at the beginning of the pandemic implicated that the SARS-CoV-2 could spread vertically based on the detection of immunoglobulin M Ab specific to SARS-CoV-2 from the neonatal blood following birth, as well as aggravated immunoglobulin G (IgG) and inflammatory cytokines.<sup>162,163</sup> However, with the increase of cases and the improvement of supervision system, the majority of studies believed that vertical transmission of SARS-CoV-2 should be rare.<sup>164–166</sup> No neonatal infection with SARS-CoV-2 was proved in a recent study involved in 43 pregnant cases with COVID-19 on the first day of life.<sup>167</sup> Perinatal transmission of SARS-CoV-2 still needs further validation owing to several unaddressed technical issues. First, for most congenital viral infections, immunoglobulin M is not a reliable criterion to diagnose an intrauterine infection due to low sensitivity and specificity, which may cause an unpredicted high rate of false positive.<sup>168</sup> Additionally, a solid proof of vertical transmission of pathogens such as ZIKV requires the isolation of viral RNA in fetal or placental tissues within the sterile intrauterine environment and/or in the newborn.<sup>169,170</sup> To exclude horizontal transmission during vaginal delivery and potential virions contamination due to intimate contact, an adequate range of biological samples from both mother and neonate (including neonatal nasopharyngeal or rectal swabs, serum, placenta, amniotic fluid, umbilical cord blood, and vaginal secretions) should be included and tested, which could reflect the authenticity of vertical transmission more precisely. Unfortunately, according to the transplacental transmission classification system, there has been no report showing the virus particles can be isolated from the fetus so far.<sup>170</sup> Therefore, the direct and convincing evidence of SARS-CoV-2 transplacental infection is still lacking.

### Other emerging viruses

Some other emerging viruses, such as Ebola virus, Rift Valley fever virus (RVFV), and West Nile virus (WNV), may also threaten maternal and fetal health through underappreciated mechanisms. For instance, RVFV, as an arbovirus, is strongly associated with fetal loss and/or stillbirth in pregnant domesticated animals, where some same outcomes have been observed in pregnant women infected by RVFV.<sup>171–173</sup> In humans, RVFV could infect placental cytotrophoblasts (CTBs) and STBs in ex vivo experiment, which could highlight the possibility of vertical transmission.<sup>174</sup> Indeed, the maternal-fetal transmission of RVFV in the third trimester was reported in a case study, while the specific transplacental route of RVFV is still unclear.<sup>172</sup> Additionally, several studies have demonstrated the maternal-fetal transmission of WNV, and the corresponding abnormalities in the central nervous system like CZS induced by ZIKV.<sup>175,176</sup> Human placental extravillous trophoblasts (EVTs) are permissive to WNV infection, which may disseminate the virus to fetus.<sup>175</sup> In

general, the emerging virus infection during pregnancy brings great challenges to a healthy pregnancy, which should be a prioritized research area we need to show solicitude for in the future.

### Placental defense mechanisms

The nosogenesis and substantial consequences resulting from viral infections during pregnancy still remain largely uncharacterized, in particular, relatively little is known about the fundamental biology behind the vertical transmission of viruses. Although it has been widely accepted that the placenta acts as a defensive barrier against viral insults, the molecular mechanisms underlying control of placental infection are still poorly understood. Several hypotheses have been proposed to explain how the placenta avoids viral infections under normal conditions based on human and mouse studies, which include but not limited to the physical or anatomical defenses, intrinsic cellular mechanisms, the constitutive release of antimicrobial immunomodulators, and so on<sup>8</sup> (Fig. 2). Moreover, great progress has been achieved regarding the transplacental transmission and pathogenesis of TORCH pathogens, especially those advanced insights obtained in animal models.<sup>3,4,177,178</sup> In this section, we will highlight molecular and cellular signatures of the placenta barrier function, which not only illustrate the etiology of vertical transmission but also shed light on the foundation of possible new therapeutic approaches to mitigate viral infection-related diseases during pregnancy.

### Cellular structure of human placenta and the corresponding susceptibility to viral infections

The structure of human placenta consists of both floating villi and anchoring villi. A continuous single layer of multinucleated STBs sets up the outer lining of floating villous tree that is in direct contact with maternal blood flowing into the intervillous space, which is critical to facilitate maternal/fetal exchange of gases, waste products, and nutrients. Furthermore, the STBs are also a major cell type undertaking the endocrine function of human placenta to drive the physiological and metabolic adaptations to pregnancy. Underneath the STB layer is the undifferentiated, mononucleated CTBs, which are anchored to a basement membrane within the placental villus. The CTBs have high proliferative capacity and form a monolayer of polarized stem cells, which eventually differentiate via cell-cell fusion into STBs that cover the entire villous surface. Another subtype of differentiated CTBs can invade and remodel the decidualized endometrium, where they are termed EVT<sub>s</sub>.<sup>6,179–182</sup> Moreover, EVT<sub>s</sub> are unique in their immune-privileged status as they are coated with self-antigens including the major histocompatibility antigen, human leukocyte antigen G, which is expressed almost exclusively in EVT<sub>s</sub> and is implicated in the maintenance of immune tolerance.<sup>183</sup>

Different subtypes of trophoblasts exhibit differential susceptibilities to pathogenic infections. Although the mechanisms are still poorly understood, the STBs have been shown to resist infections by diverse pathogens. For instance, in human placental explant cultures, cytomega-

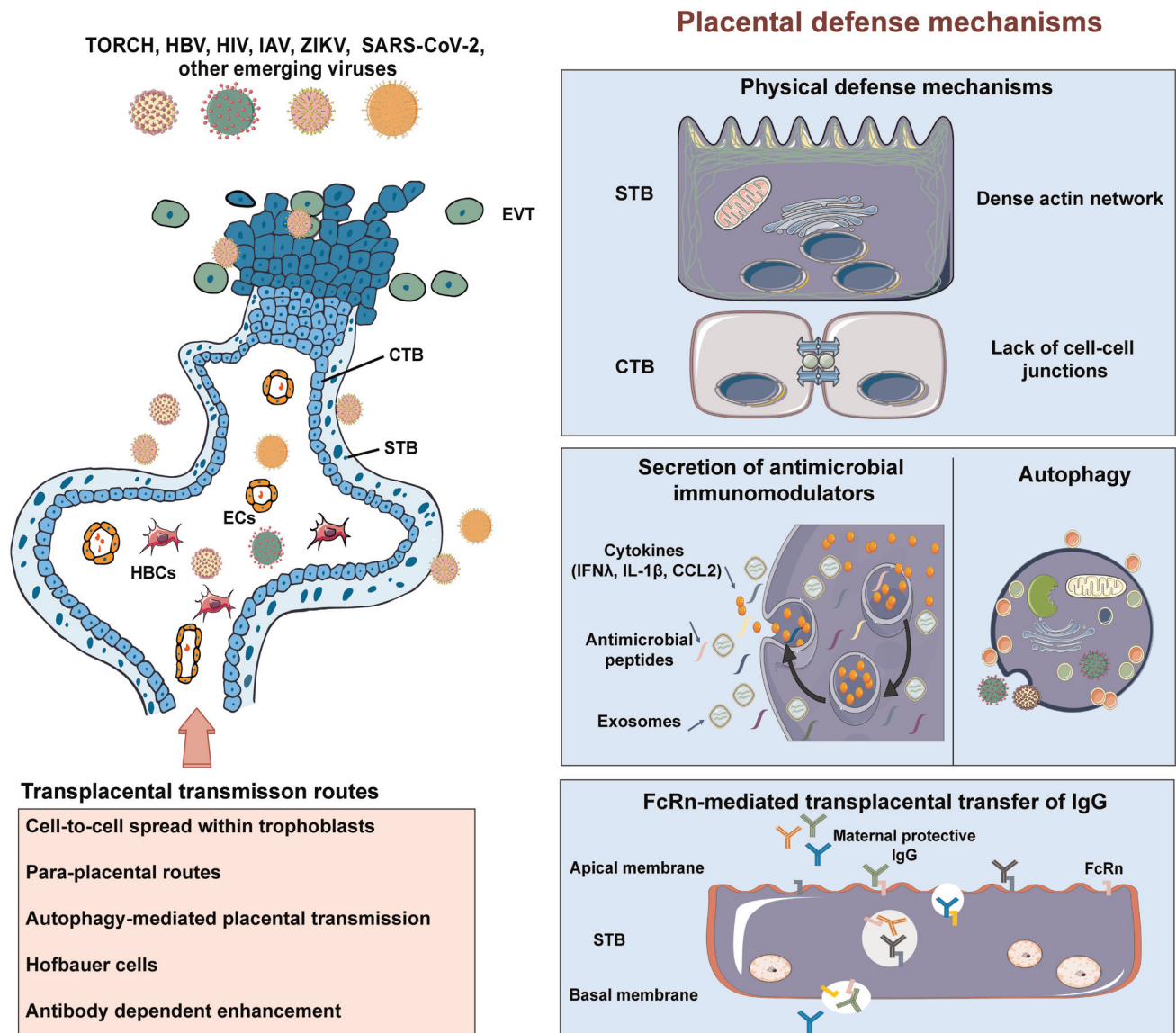
loviruses could preferentially infect CTBs verse STBs.<sup>184,185</sup> Nevertheless, in the recent pandemic, it was proposed that SRAS-CoV-2 prefers to target STBs probably due to high abundance of viral receptors on their apical surface.<sup>161,186</sup> EVT<sub>s</sub> are known to be more sensitive to bacterial and viral infections than the CTBs and STBs, but the mechanisms underlying this observation are not well defined.<sup>187</sup> Indeed, in naturally infected human term placentas, most cytomegalovirus is predominantly found in the EVT<sub>s</sub>.<sup>188,189</sup> Moreover, chorionic villus explants from first-trimester placentas have confirmed that ZIKV appears to bypass the STBs to reproducibly replicate in EVT<sub>s</sub>.<sup>113,190</sup> They are the most plausible hosts to pathogens maybe due to the fact that these cells express human leukocyte antigen G and may provide a protected niche for viral reservoirs.<sup>191</sup> In addition to trophoblasts, leukocytes derived from maternal compartments, including decidual NK cells, macrophages, T cell subsets, and placenta-specific macrophages—the HBCs, not only play a key role in maintaining the immune tolerance feature of normal pregnancy but also have some complex mechanisms for removing pathogens or as a “Trojan Horse” for viral vertical transmission. For example, decidual NK cells could limit HIV infection in decidual macrophages by the contact-dependent cytolysis and IFN release. On the contrary, a higher permission of HBCs to ZIKV infection could promote the dissemination of ZIKV within fetal compartments.<sup>116,192,193</sup>

### Physical defense mechanism

By term, owing to extensive branching morphogenesis of placenta villi during 9 months of gestation, the overall epithelial surface area of STB layer reaches approximately 12–14 m<sup>2</sup>, which forms the frontline of placental defense restricting the hematogenous spread of pathogens.<sup>177</sup> Physical characteristics of placenta syncytium that naturally confers microbial resistance cover the brush border formed at the apical surface of STB layer, the diminished cell–cell junctions, and condensed cortical actin network.<sup>194,195</sup> Cell–cell junctions, intercellular seal structures formed by various transmembrane proteins coupled with cytoplasmic adaptors, are essential components of the epithelial fence, which were weakened or exploited by many pathogens in the process of traversing epithelial barriers.<sup>195</sup> Therefore, lack of cell–cell junctions in STBs may be beneficial for blocking pathogens from a gateway to fetus in general. The unique cytoskeletal organization of the STB (such as disordered mesh of actin microfilament) conduces to its elasticity, while obstruction of this feature promotes microbial infections. It should be noted that pathogens accessing to fetus also should overcome the defensive functions of the cells embedding in villous stroma like microvasculature of fetal blood vessels.<sup>8</sup>

### Autophagy

Autophagy is established to be a vital part of the host immune response to microbial infection and is considered to directly eliminate intracellular pathogens by mediating their delivery to lysosomes.<sup>196</sup> Trophoblast cells exhibit a high basal autophagy level at term, which could be used as a pan-antimicrobial strategy to limit the replication and



**Figure 2.** Placental defense mechanisms against viral infections. The human placenta exploits disparate cellular and molecular mechanisms of antiviral defense, which encompasses the physical or anatomical defenses, constitutive release of antimicrobial immunomodulators, autophagy and FcRn mediated antibodies transplacental transfer. CCL2: C-C motif chemokine ligand 2; CTB: Cytotrophoblast; ECs: Endothelial cells; EVT: Extravillous trophoblast; FcRn: The neonatal fragment crystallizable receptor; HBCs: Hofbauer cells; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; IAV: Influenza A virus; IFN $\lambda$ : Interferon  $\lambda$ ; IgG: Immunoglobulin G; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; STB: Syncytiotrophoblast; TORCH: Toxoplasma, Others, Rubella, Cytomegalovirus, and Herpes simplex virus; ZIKV: Zika virus.

transplacental transmission of various pathogens.<sup>197,198</sup> Consistent with this idea, dysregulated autophagy has been characterized in malaria- and bacteria-infected human placenta samples.<sup>199,200</sup> However, major pathogens, known to induce transplacental infection, can evade or subvert autophagic cellular machinery to survive or replicate intracellularly. Recently, we have demonstrated that vertical transmission of ZIKV was significantly reduced in autophagy-deficient mouse models, consistently, treatment of autophagy inhibitors also hindered placental and fetal ZIKV infection and rescued the corresponding poor pregnancy outcomes.<sup>201</sup> In summary, the effects of autophagy in terms of transplacental infection might be highly dependent on the pathogens involved.

**Secretion of antimicrobial immunomodulators**

Aside from the protective architecture of human placental, trophoblasts possess the robust innate immune activity and secrete antimicrobial molecules to limit infection. We and others proved that trophoblast-derived IFNs confer complex protection from viral infections. IFN- $\alpha$  receptor knockout mice recapitulate the maternal and fetal phenotypes of transplacental ZIKV infection.<sup>117</sup> However, hyperactivated type I IFN signaling in response to live virus or viral mimics could result in detrimental outcomes to fetus including fetal demise and IUGR, which is at least partly due to deficient trophoblast syncytialization caused by IFN induced trans-membrane proteins.<sup>202-204</sup> Therefore, the activation of type I IFNs in placenta in response to infectious signals is a double-edged sword with regards to



pregnancy outcomes. Type III IFNs (including interferon  $\lambda$  (IFN $\lambda$ 1), IFN $\lambda$ 2, and IFN $\lambda$ 3) also confer resistance to ZIKV infection in both mice and human placenta, which may partially explain distinct vulnerability to ZIKV infection in placentas from different gestational ages. Exogenous prophylactical and therapeutic IFN- $\lambda$  treatment has been proposed against vertical transmission in the setting of ZIKV as well.<sup>205</sup>

The Toll-like receptors, Retinoic acid-inducible gene I-like receptors, and nucleotide-binding oligomerization domain-like receptors are pattern recognition receptors expressed at the maternal-fetal interface throughout pregnancy, whose expression exhibit both temporal and cell type specific fluctuations. The activation of antiviral signals downstream of pattern recognition receptors triggers a potent defense mechanism utilized by placenta cells to effectively protect the fetus from pathogen attacks through producing large amounts of pro-inflammatory cytokines and chemokines such as tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and C-C motif chemokine ligand 2.<sup>206,207</sup> Indeed, the inhibition of inflammasome signaling could robustly sensitize trophoblasts to the infection of *Listeria monocytogenes* in human placental explants, highlighting cytokines secreted from placenta could limit infections. However, detrimental actions of interleukin-1 $\beta$  and other pro-inflammatory cytokines in infected placentas are involved in adverse neonatal outcomes, suggesting that tightly regulated immune responses are crucial to sustain placenta homeostasis.<sup>208</sup> Besides, human trophoblasts-associated antiviral microRNAs, such as chromosome 19 miRNA cluster that are packaged into placental exosomes, were also systemically isolated from pregnant women, which operate in a paracrine or autocrine manner to resist infection.<sup>209,210</sup> Mechanistically, primary human trophoblast-derived chromosome 19 miRNA cluster family members drastically limited both RNA and DNA viral infections in non-placental cells by inducing autophagy, demonstrating a unique placenta-secreted effector for shielding virus-sensitive cells in placenta from infections.<sup>198,211</sup>

### **The neonatal fragment crystallizable receptor (FcRn) mediated antibodies transplacental transfer**

Transplacental passage of IgG begins in the first trimester of pregnancy and lasts until labor, which sets up another layer of fetal protection from viral infections.<sup>212</sup> Generally, endocytosis of IgG from maternal blood was initiated by binding to a canonical IgG shuttle receptor, FcRn, on the apical side of STBs. Furthermore, a successful transplacental transfer of IgG must cross other two barriers: the villous stroma and the fetal endothelium. However, fibroblasts, HBCs, and fetal endothelial cells do not express FcRn, which remains somewhat a knowledge gap regarding IgG transfer.<sup>213</sup> Some noncanonical Fc receptors, such as Fc $\gamma$ RIII and Fc $\gamma$ RII, may be engaged in transplacental IgG transfer as well.<sup>213</sup> Recent findings revealed that the selective transfer of maternal IgG traversing placenta involved a panel of risks, including antigen, IgG subclass, and glycan profile, which simultaneously determine the efficient placental transfer of maternal antigen-specific IgG.<sup>214</sup> For example, Jennewein *et al.*<sup>215</sup> demonstrated that di-glycosylated Fc-glycans of antigen-specific antibodies, selectively binding to FcRn

and FCGR3A, were preferentially passed across the placenta. Future studies defining the determinants and mechanisms of placental IgG transportation will generate possible new strategies to improve the transfer of maternal IgGs to the vulnerable fetus and fundamentally mitigate viral infection-related diseases.

### **Conclusions and prospects**

The mechanisms contributing to maternal and fetal damages due to viral infections are complex and highly depend on various pathogenesis factors such as the infectious power of certain viruses, tissue and cellular tropism, and host-pathogen interactions in the placenta niche. Sustained research efforts on understanding how maternal physiological adaptations to pregnancy govern different susceptibility to certain viral infections are needed. Besides, much remains to be learned about the fundamental and unique features of placental defense mechanisms that can help us to cope better with emerging viruses to avoid congenital diseases during pregnancy, which is especially critical in the context of vertical transmission. Comprehensive clinical and basic studies uncovering the etiological nature of viral infections during pregnancy can empower us with countermeasures to face new viral epidemics that cause known and unanticipated maternal and fetal complications. Foundational research on the development of antiviral treatments and vaccines effective in the pregnant population with no safety concern should be prioritized as a powerful weapon to fight the next epidemics and pandemics.

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### **Author Contributions**

Wenzhe Yu, Xiaoqian Hu, and Bin Cao prepared the figures and drafted the manuscript. All authors reviewed the final manuscript and had no dissent on the submission.

### **Conflicts of Interest**

None.

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