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MINIREVIEW

Role of Inflammation in Virus Pathogenesis during Pregnancy

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ABSTRACT Viral infections during pregnancy lead to a spectrum of maternal and fetal outcomes, ranging from asymptomatic disease to more critical conditions presenting with severe maternal morbidity, stillbirth, preterm birth, intrauterine growth restriction, and fetal congenital anomalies, either apparent at birth or later in life. In this article, we review the pathogenesis of several viral infections that are particularly relevant in the context of pregnancy and intrauterine inflammation. Understanding the diverse mechanisms employed by viral pathogens as well as the repertoire of immune responses induced in the mother may help to establish novel therapeutic options to attenuate changes in the maternal-fetal interface and prevent adverse pregnancy outcomes.

KEYWORDS inflammation, pregnancy, viral infection

Viral infections during pregnancy are known to increase risks for miscarriages, preterm birth, stillbirth, fetal brain injuries, intrauterine growth restriction, hearing loss, cataracts, and other fetal abnormalities (1–4). During maternal infection, the placenta serves as an immune organ, protecting the fetus from pathogens. However, viruses have evolved complex mechanisms to induce disease, while heightened maternal immune cytokine activation in response to infection also results in detrimental effects on the fetus.

Specific viruses, among other pathogens, have been established to be associated with adverse pregnancy outcomes and congenital defects, constituting parts of the acronym TORCH (toxoplasma, others, rubella, cytomegalovirus [CMV], and herpes). "Others" includes Zika virus (ZIKV), parvovirus B19, human immunodeficiency virus (HIV), hepatitis viruses, and more (3, 5). More recently, researchers have also proposed including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this acronym (6). Some congenitally acquired viral infections are more common. For example, CMV, the most common cause of congenital birth defects, reaches 800/1,000,000 live births in the United States (worldwide data are unavailable), while other viruses are less prevalent: hepatitis B reaches $<$0.1/1,000,000 U.S. population and 240 million worldwide, and HIV reaches 162 infants/year (2010) in the United States and 35.3 million worldwide (3). Among the aforementioned TORCH pathogens, there are vaccine-preventable viruses, which still represent a great burden in low- and middle-income countries, resulting in adverse pregnancy and neonatal sequelae. For example, while cases of congenital rubella syndrome (CRS) were vastly underreported, it was estimated that CRS affected 46,000 infants annually in Southeast Asia alone (1).

Between 2.2 and 8.4% of even asymptomatic pregnant women with normal ultrasound findings have detectable viral genomes in the amniotic fluid. At least one of the eight viruses was found to be adenoviruses, herpes simplex virus (HSV), varicella-zoster virus (VZV), human herpesvirus 6 (HHV6), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), parvovirus B19, and enteroviruses (1, 7). HHV6 was the most common virus detected in amniotic fluid, at 1%. In this study, viruses were not associated with any changes of the white blood cell counts or cytokine levels, but they can be a predis-

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posing factor to intrauterine inflammation with other pathogens, so further studies are needed (1, 7). Intrauterine inflammation is known to be a predisposing factor to adverse maternal (preterm birth) and fetal (perinatal brain injury in the form of periventricular leukomalacia) outcomes.

Certain infections may disproportionately affect pregnant compared with nonpregnant women (8). Pregnant women are more severely affected by some viral infections, including influenza virus, hepatitis E virus (HEV), and HSV. One of the recent theories proposed that a shift from Th1 to Th2 immunity during pregnancy suppresses the $CD4^+$, $CD8^+$, and natural killer (NK) cell response, decreasing the robustness of cell-mediated immunity against viral infection (8–10). However, the pathophysiological basis of this increased susceptibility still is not well understood, and the evidence of increased susceptibility of pregnant women to infection is rather weak. These responses may be relevant to a heightened inflammatory mechanism and the Th immune shift.

Our review focuses on the pathogenesis of virus-induced inflammation and its maternal and fetal adverse outcomes. Understanding the mechanisms employed by viral pathogens in the placenta and fetus and studying the gaps in the current research may enable new therapeutic approaches to decrease the adverse pregnancy outcomes and fetal anomalies and improve fetal survival.

METHODOLOGY

We conducted a comprehensive search of peer-reviewed journal articles indexed in the NLM's MEDLINE and PUBMED databases, available as of 15 May 2020, using the following search terms: "viral infections and pregnancy," "viral infections and neonatal outcomes," and "viral infection pathogenesis in pregnancy." We also searched each of these terms separately for certain viral pathogens of interest for pregnancy. Manual searches of reference lists from relevant papers were performed to identify additional studies. While all studies and review articles were evaluated and reviewed, we mostly focused our review on the clinical outcomes of the viral infections of mother and fetus and the possible immunologic mechanisms of invasion (Table 1).

DNA VIRUSES AND PREGNANCY

CMV, or herpesvirus type 5, is a member of the *Betaherpesvirinae* subfamily and persists lifelong following primary infection (11). The specific immunologic mechanisms controlling lifelong latency of the disease and the possibility of reinfection with a new CMV strain are not well understood (12). Human CMV is the most common cause of congenital infection, affecting 0.2 to 2% of all live births (12). Congenital CMV transmission rates are as high as 50% in women who acquire primary CMV infection during pregnancy and less than 2% in women with nonprimary infection (13). The two known main sources of primary CMV infection during pregnancy are through sexual activity and contact with young children, where infection transmission can occur *in utero*, intrapartum, and during breastfeeding (14). Among the mentioned sources, *in utero* CMV transmission has the highest risk of congenital infection (15). The severity of congenital CMV infection decreases with advancing gestation; however, the risk of transmission to the fetus rises from 40% in first and second trimesters to 60% in the third trimester (16). Interestingly, even the occurrence of primary CMV infection in the preconception and periconception periods have been associated with increased risk of *in utero* CMV transmission (5% and 16%) (17).

According to several studies, women who did not transmit CMV to the fetus had earlier production of neutralizing antibodies against CMV (gH/gL/pUL128L) (18) in addition to an early $CD4^+$ response (19). Furthermore, it was found that decreased reexpression of CD45RA on the surface of HCMV-specific effector memory cells correlates with HCMV transmission to the fetus (20). In the placenta, CMV replicates in differentiating cytotrophoblasts (CTB), where it induces downregulation of matrix metalloproteinase-9 (MPP-9) and integrin $\alpha_1\beta_1$, impairing cell invasiveness (21). The resultant impairment of cytotrophoblast integrity facilitates the spread of the virus to

TABLE 1 Cytokines and signaling pathways

Virus type	Description
DNA virus	
HSV	CMV infection triggers innate immune responses resulting in IFN-γ production within the maternal decidua; CMV may stimulate the secretion of various cytokines in the placenta, including IFN-γ, which in turn promotes β2MG production in the fetus
	In maternal serum, inflammatory markers CPR and SAA are increased
	In placenta, MPP-9 and integrin $\alpha1\beta1$ are downregulated
	In fetus, the virus exhibits tropism to neural cells and activates an inflammatory response in fetal brain
	HCMV interacts with TLR2 on ST-like cells, consequently stimulating the production of TNF-α
	β2MG, which is produced by activated lymphocytes and accelerated by inflammatory cytokines, such as IFN-γ, is significantly increased in FGR newborns' urine with placental CMV detection
	Adaptor protein stimulator of interferon genes (STING) is essential for IFN-β induction by HSV-1; increased expression of IFI16 and RIG-I has been observed following HSV-1 infection in human third-trimester placenta, which recognizes dsDNA to induce type I IFNs, the STING/TBK1/IRF3 pathway, and proinflammatory cytokine responses via the NF-κB pathway
	Mitochondrial checkpoints have been reported to initiate NF-κB activation in the macrophage after HSV infection
	In placenta, there is inhibition of IFN-β expression or enhanced expression of cellular receptors, including both TAM ligand and TAM receptors
	IL-12, along with numerous cytokines, induces the production of IFN-γ, mainly in NK cells, to trigger killing of infected cells
	HSV inhibits the expression of several proinflammatory cytokines, including IFN-α/β, TNF-α, IL-6, IL-12, and RANTES, by reducing the stability of mRNA in macrophages
VZV	IFN-α, IL-1α, IL-6, CXCL10, and TGF-β are produced by VZV-infected fetal DRG, but exact cellular source of these cytokines is unknown; DRG infection is also associated with increased TGF-β and TGF-β-related cytokines
RNA virus	
Influenza viruses	Systematically, there are lower circulating levels of IgG2 following infection of H1N1 during pregnancy
	Pregnant women with H1N1 exhibit an attenuated innate interferon response
	In pregnant mice with H1N1, there is a prominent association between mortality and induction of proinflammatory cytokines and chemokines (TNF-α, CCL2, CCL3, and CXCL1)
ZIKV	Systemic inflammatory response consists of increased IL-1β, IL2, IL6, IL7, IL15, and IL16
	ZIKV infection leads to the inhibition of type I IFN production and downstream ISGs
	ZIKV NS1, NS4A, and NS4B proteins function as the primary suppressors of type I IFN induction by blocking TBK1/IRF3 pathways
	Damaged fetal brain indicates significantly higher expression of NLRP1, NLRP3, AIM2, IL-1β, IL-6, IL-18, IL-33, and caspase 1 following ZIKV-induced inflammation
HIV	During maternal HIV-1 infection, maternal neutralizing antibodies (NAbs) and virions interact directly with placental macrophages (Hofbauer cells) prior to entering fetal circulation; Hofbauer cells express HIV-1 (co)receptors CD4, CCR5, CXCR4, and DC-SIGN on their surface and sequester Abs and Ab-virion immune complexes, limiting HIV-1 MTCT
	Additional host restriction factors expressed by HCs or trophoblasts have been identified, including APOBEC3G and ISGs
	Phagocytes (neutrophils, monocytes/macrophages, and DCs) and other innate immune cells (such as plasma cell-like DCs and IFN and NK cells) are initially recruited to eliminate the virus
	IP-10 (also called CXCL10, a CXC chemokine) increases, which is associated with low CD4 counts
	The major immune cells and associated cellular mediators in HIV-1 infection include (i) dendritic cells (cDC and pDC), macrophages, and NK cells (IFN-γ, IFN-α, IL-6, IL-7, IL-10, IL-12, IL-15, IL-18, IP-10, MCP-1, and TNF-α) and (ii) $CD4^+$ T cells (Th1, Th17, Treg, and Tfh), $CD8^+$ T cells, and B cells (IFN-γ, IL-7, IL-12, IL-15, IP-10, MIP-1β, RANTES, and A-SAA)
	Plasma CXCL13 levels increase during early and chronic HIV infection
	The level of sTNFR2 and IL-6 change in pregnant women's serum; MiP is associated with increased sTNFR2, sICAM-1, and IL-18BP concentrations during pregnancy
	There is a lack of correlation between maternal and neonatal inflammatory markers, suggesting that these biomarkers do not cross the placenta during HIV infection
HCV	Maternal-fetal tolerance mechanisms can induce an inhibitory effect on cellular immunity to suppress HCV-specific CTL activity, preventing hepatocyte destruction
	The placenta releases endogenous IFN-α during pregnancy, which can influence ALT levels
	Newborns exposed to HCV have activation of inhibitory T cells and proinflammatory markers, which are offset by higher IFN-γ production
	Human trophoblast cells infected with HCV-RNA can induce strong upregulation of type I/III IFN and increased expression of chemokines, such as CCL5 (RANTES), CXCL10 (IP-10), and CXCL11 (I-TAC), inducing the recruitment and activation of decidual NK cells; HCV-RNA transfection could induce apoptosis in HTR8 cells, which may affect morphology of placenta
	Gradient of the proportion frequency of NKT and $\gamma\ \delta$-T cells in placenta is higher than that in umbilical cord blood
	Polymorphisms of IL-28B promoter, mannose-binding lectin, TNF-α, IFN-γ, IL-10, and TGF-β have also been used to study the risk of MTCT of HCV

(Continued on next page)

TABLE 1 (Continued)

Virus type	Description
	Infected hepatocytes secrete cytokines, such as IL-8, CXCL-9, and CXCL-10, all of which are associated with previous damage, to recruit T cells to the infected liver
	Liver TNF-α is associated with increased inflammatory activity, liver fibrosis, and liver injury in patients with chronic hepatitis C
	In patients with mixed infection of HCV and HBV, the roles of IL-6 and IL18 are vital, and the effect of interferon on immune status could be evaluated
	Serum mediators, such as IL-6, IL-8, CXCL-9, CXCL-10, CXCL-12, and macrophage MIF, are increased
RV	The virus enters the fetus via the maternal bloodstream and infects the epithelium of chorionic villi and the endothelium of the blood vessels of the placenta
	RV induces apoptosis in monolayers of human normal-term placental CVE and CTB
	Inflammatory chemokines have been observed to be increased in the supernatant of RV-infected endothelial cells
	The level of IFNs induced by RV strain in placenta is significantly changed
SARS-CoV-2	Virus enters alveolar epithelial cells via the membrane-bound ACE2 receptor, which may cause pneumonia, sepsis, or aspiration due to cytokine storms, including cytokines IL-6, IL-2, IL-7, IL-10, TNF-α, G-CSF, MIP1A, MCP1, and IP10
	Patients with COVID-19 reveal activation of both Th1 and Th2 immunity, culminating in the presence of IFN-γ and IL-1β as well as IL-4 and IL-10
	Elevated levels of IL-6 (a predominantly Th1 response) are associated with a significantly increased risk of mortality
	Th1 cell-mediated immunity attenuates due to the physiological transition to a Th2 dominant environment; Th2 dominant environment and hormonal milieu tend to increase the expression of anti-inflammatory cytokines (IL-4 and IL-10) and other unidentified immune adaptations, which may take responsibility for the predominant immune response to SARS-CoV-2, resulting in the lesser severity of COVID-19 compared to that in nonpregnant patients
	Changes of the hormonal milieu in pregnancy would influence immunological responses to viral pathogens

the fetal compartment. Within fetal tissues, the virus exhibits tropism to neural cells. However, the neuropathogenesis of CMV-induced brain disorders has not yet been fully elucidated. It was observed that HCMV-infected cells localize predominately in the ventricular and subventricular zones (SVZ) (22), where the virus disrupts the functions of neural stem cells (23).

The primary infection during pregnancy is asymptomatic in 75 to 95%; alternatively, it can manifest as a mild mononucleosis or flu–like syndrome with persistent fever, fatigue, and a variety of eruptions (in one-third of patients), with rare incidence of CMV-induced organ-specific complications (24). There is no evidence that pregnancy can increase maternal CMV disease severity, but cervical shedding may be more common among pregnant women: 5% in the first trimester, 6% to 10% in the second trimester, and 11% to 28% in the third trimester (25). Furthermore, 30% of seropositive women intermittently secrete CMV in the breastmilk.

Most infants with congenital CMV are asymptomatic at birth. Congenital CMV is the leading cause of nonhereditary sensorineural hearing loss, growth failure, and vision loss (26). The clinical findings of symptomatic congenital CMV infection include jaundice, petechiae, thrombocytopenia, hepatosplenomegaly, growth restriction, myocarditis, and nonimmune hydrops (15). Both symptomatic and asymptomatic children excrete the virus for several years after birth, whereas in adults, viral excretion is usually controlled within several months. This reduced control of CMV replication suggests a limitation in cell-mediated immune responses of infants. Around 10% to 15% of asymptomatic infants will develop long-term neurological sequelae, primarily hearing loss (12, 26).

One study (27) indicates that chronic villitis was commonly observed in the placentas with CMV infection. Studies demonstrate CMV antigens induce placental inflammation in a Toll-like receptor-2 (TLR2)-dependent manner as an innate defense response instead of a direct infection (28, 29). Specifically, HCMV interacts with TLR2 on syncytiotrophoblast (ST)-like cells, consequently stimulating the production of tumor necrosis factor alpha (TNF-α) and inducing the apoptosis of adjoining cells.

In addition, placental inflammation caused by CMV-induced chronic villitis results in the elevation of inflammatory markers in the serum of pregnant women. One cohort study (27) demonstrated that increased C-reactive protein (CRP) or serum amyloid A (SAA) levels in the serum was frequently discovered in fetal growth restriction (FGR) cases with placental CMV detection, indicating that CRP and SAA can serve as biomark-

ers to predict CMV-induced placental inflammation during pregnancy. Intrauterine growth restriction in light of placental CMV infection may be attributed to the intrauterine inflammation without vertical transmission of the virus.

Furthermore, beta-2 microglobulin (β2MG), which is produced by activated lymphocytes and accelerated by inflammatory cytokines, such as gamma interferon (IFN-γ), was significantly higher in FGR newborns' urine with placental CMV detection (27). Previous reports (27, 30, 31) suggest that β2MG is an efficient diagnostic marker for symptomatic CMV congenital infections. CMV infection could trigger innate immune responses, resulting in IFN-γ production within the maternal decidua (32). Thus, CMV may stimulate the secretion of various cytokines in the placenta, including IFN-γ, which in turn promotes β2MG production in the fetus.

All in all, the inflammatory biomarkers in the serum of pregnant women may be useful in establishing a diagnosis of placental chronic villitis induced by CMV. Maternal CMV serologic tests may also be important to comprehensively predict the possibility of congenital CMV infection.

Antiviral treatment prenatally and postnatally was not proven to be effective at preventing congenital or postnatal CMV infection. There are several studies that found antiviral treatment with ganciclovir to be effective in the treatment of symptomatic congenital CMV infection, indicating improved neurologic outcomes compared to those of nontreated groups (33).

HSV. Herpes simplex virus (HSV) belongs to the *Herpesviridae* family. HSV infection is prevalent worldwide among women of childbearing age. There are two groups of diseases caused by HSV. The orolabial herpesvirus infection, mostly caused by HSV-1, usually occurs in young children and results in asymptomatic infection. Genital HSV infection, one of the most common sexually transmitted diseases, can be caused by HSV-2 or HSV-1. The United States National Health and Nutrition Examination Survey (NHANES) estimated that the seroprevalence of HSV-1 and HSV-2 in pregnant women from 2007 to 2014 is 59.3 and 21.1% (34). Latency and neurovirulence are the most important biologic properties of HSV infection for humans, where the virus will persist lifelong in the sensory ganglia following primary infection.

HSV infections have similar clinical presentation in pregnant and nonpregnant women, usually asymptomatic or associated with mild symptoms. The orofacial HSV is associated with single or clustered vesicles on the face and lips, while genital HSV vesicles are located on the genitalia, perineum, buttocks, upper thighs, or perianal areas. HSV rash can ulcerate before resolving. The symptoms of primary HSV infection may include malaise, fever, or localized adenopathy. However, transmission of genital herpes to the fetus results in neonatal infection, causing serious morbidity and mortality (35).

HSV is transmitted mainly through direct contact with infected individuals but also can be transmitted to infants from infected pregnant mothers (35). Neonates can be infected *in utero*, peripartum, and postpartum. Peripartum transmission is most common (~85%), while *in utero* has the lowest probability of transmission (5%) (32). Intrauterine HSV infection can be acquired from maternal viremia and is associated with primary HSV infection or ascending infection during pregnancy.

There are three clinical groups of genital HSV infections: primary, nonprimary first episode, and recurrent. Primary maternal genital HSV infection poses the highest risk of neonatal transmission at delivery, while the recurrent HSV infection is the most common form. Primary genital HSV-2 infection is more common; furthermore, it has a higher rate of reactivation. Almost 100% of women with HSV-2 experience clinical or subclinical recurrences throughout their lives. Perinatal transmission is almost the exclusive cause of neonatal HSV-2, occurring as mucocutaneous lesions and/or central nervous system (CNS) disease (36–38). Neonatal HSV can be divided into three main categories: local skin, eyes, and oral cavity (SEM); with or without SEM CNS; and transmitted diseases.

During pregnancy, HSV infection is associated with spontaneous abortion, intrauterine growth restriction, preterm delivery, skin scars, chorioretinitis, and microphthalmia (30). The infection that occurs early during pregnancy poses a higher risk, but it may also have severe fetal consequences in late gestation (31).

The intrauterine infection caused by primary HSV infection with viremia in pregnant women is associated with placental infarction, necrotizing calcifying mycosis (inflammation of the umbilical cord), plasma cell infiltration (39), fetal hydrops, and even death *in utero*. The neonate may have the characteristic triad of skin vesicles, ulcers, and scars, eye injuries, and severe abnormalities of the CNS, including microcephaly or edema.

Ascending infection usually occurs after prolonged rupture of fetal membranes in mothers with HSV infection near the active stage during delivery. Sometimes it occurs in the absence of a ruptured amniotic membrane (40). The cellular targets in herpesvirus are epithelial cells of skin and mucosa and neurons. In terms of pathogenesis, HSV infection can lead to loss of HLA-G, since the virus can block HLA-G intracellular transport in placenta (41). HSV can infect human trophoblast cells, leading to cell death or reduced secretion of human chorionic gonadotropin (42).

Aldo et al. (2) proposed that HSV-2 infection could lead to an increased sensitivity of trophoblast cells to ZIKV infection via inhibition of IFN-β expression or enhanced expression of cellular receptors required for ZIKA entry, including both TAM (members of the phosphatidylserine receptor family) ligand (Gas6) and TAM receptors (Axl, Mer, and Tyro), which facilitate ZIKV entry into trophoblast cells. Several reports have shown that HSV-1 DNA and double-stranded RNA (dsRNA), a side product of viral replication, are detected by various kinds of pattern recognition receptors (PRRs), which play a significant role in the maternal-fetal interface (2–11). In addition, it was demonstrated that the adaptor protein stimulator of interferon genes (STING) is essential for IFN-β induction by HSV-1 (2, 12). Increased expression of IFI16 and RIG-I was observed following HSV-1 infection, and double-stranded DNA (dsDNA) to induce type I IFNs via the STING/TBK1/IRF3 pathway and proinflammatory cytokine responses via the nuclear factor kappa B (NF-κB) pathway were recognized (43). Mitochondrial checkpoints have been reported to initiate NF-κB activation after HSV infection (44). These studies indicate the ability of cellular pathogen sensors to induce downstream signaling pathways in response to viral infection and to prevent immunological rejection of the fetal allograft in order to decrease the incidence of stillbirth and preterm birth. However, HSV is capable of inhibiting the expression of several proinflammatory cytokines, including IFN-α/β, TNF-α, IL-6, IL-12, and RANTES, by reducing the stability of mRNA. Thus, HSV can hinder the host's antiviral response to infection (45). IL-12, along with numerous cytokines, induces the production of IFN-γ, mainly in NK cells, to trigger killing of infected cells (46).

Chickenpox virus/VZV. Varicella (chickenpox) infection is caused by a highly infectious DNA virus known as varicella-zoster virus (VZV). While children exhibit only mild symptoms following infection, adults are at risk of significant complications, such as secondary bacterial infections, lesions, encephalitis, and hepatitis (47). Following primary infection, VZV is capable of remaining dormant within the sensory nerve ganglia and causes latent infection in 10 to 20% of cases via reactivation, resulting in shingles or herpes zoster (47).

In the context of pregnancy, the incidence of varicella pneumonia is similar to that of nonpregnant individuals; however, it results in significantly higher morbidity and mortality (up to 20%) in pregnant women (47, 48). Increased severity has been attributed to changes in the immunological profile during pregnancy or the mechanical effect of an enlarged uterus in restricting the movement of the diaphragm, although further studies are required (48). The ability of VZV to traverse the placenta following infection ($\sim$24%) of pregnant women and to infect fetal neurons and neuronal precursors has been shown to result in congenital defects, known as congenital varicella syndrome (CVS) and neonatal chickenpox (49). CVS is typically characterized by low birth weight and intrauterine growth restriction with occasional incidence of fetal

mortality, neurological defects, skin lesions, limb abnormalities, ocular disease, and muscular hypoplasia (48, 50). A prominent hypothesis suggests CVS is caused by the reactivation of VZV rather than primary infection, which is supported by the dermatological distribution of skin lesions and segmental maldevelopment (51). Furthermore, the immature fetal cell-mediated immunity would also shorten the latent period between primary infection and reinfection (52). Several studies have demonstrated the highest risk (up to 25%) of intrauterine infection following maternal varicella infection in the first and second trimester and CVS in around 12% of infected fetuses (48). Although there exists a theoretical risk of CVS during maternal herpes zoster infection, no cases have been reported.

The VSV viral envelope glycoprotein gE is essential for infection. This protein binds to the insulin-degrading enzyme (IDE) receptor and employs heparan sulfate to facilitate host cell infection. Various cytokines and chemokines are produced in VZV-infected fetal dorsal root ganglia (DRG), including IFN-α, IL-1α, IL-6, CXCL10, and transforming growth factor beta (TGF-β) (53). While inflammatory cytokines were increased, DRG infection was also associated with increased TGF-β and TGF-β-related cytokines (54). The exact cellular source of these cytokines is unknown, but satellite glial cells (SGC) have been hypothesized to be candidates (47). SGC are a specialized ganglionic cell type that share phenotypic and functional features with antigen-presenting cells. Cytokine changes in response to CVS in the placenta during pregnancy are unknown.

The administration of the varicella vaccines effectively reduces risk of infection, but suboptimal vaccination coverage has resulted in the susceptibility of relatively high numbers of high-risk populations, including pregnant women (48, 49). As a live vaccine, it is contraindicated in pregnant women, making antiviral therapy and varicella-zoster immunoglobulin (VZIG) the only available modes of prophylaxis/treatment for severe disease during pregnancy (55). While effective in nonpregnant individuals, controlled studies are still required to demonstrate efficacy in the context of pregnancy.

RNA VIRUSES AND PREGNANCY

Influenza viruses. Influenza viruses are a major public health burden, having caused four pandemics since 1918 in addition to annual epidemics, resulting in a substantial number of illnesses and deaths (56). They are characterized by segmented, negative-strand RNA genomes whose error-prone RNA-dependent RNA polymerases enable antigenic drift and antigenic shift (57). As a result, we are required to update the seasonal vaccine annually based on surveillance across the world to match the ever-changing antigenic domain(s) of the virus.

In addition to young children and the elderly, pregnant women are at high risk of developing severe or possibly fatal influenza infections during seasonal epidemics as well as pandemics (58, 59). Data from the 1918 H1N1 and the 1957 H2N2 pandemics have revealed increased risk of complications following influenza A virus (IAV) infection (58). More recently, during the 2009 H1N1 pandemic (H1N1pdm09), approximately 5% of total fatalities were pregnant women, while they only constituted 1% of the total population (60). In addition to adverse effects on maternal health, influenza infection may also result in adverse fetal outcomes, including fetal demise, reduced weight, and preterm delivery (58, 61). However, in most cases, vertical transmission of the virus was not observed, suggesting indirect effects of infection on fetal outcomes (62, 63).

Interestingly, women specifically in their third trimester of pregnancy were at the greatest risk of severe influenza (58, 64, 65). Over 50% of deaths due to secondary pneumonia during the 1918 H1N1 pandemic were of women in their third trimester of pregnancy (58). A similar trend was observed in the example of seasonal influenza cases between 1974 and 1993, where women in the third trimester of pregnancy were more than 3 times more likely to die due to influenza-related illness than nonpregnant women (64). While anatomical changes during pregnancy may contribute to increased severity, various physiological changes leading to altered cardiopulmonary and immunologic function are considered more significant contributors to severe outcomes. Remarkably, pregnant women without pregnancy-associated cardiopulmonary comor-

bidities were also shown to be at a higher risk of influenza-related hospitalization and death following infection, suggesting the altered immunological profile itself is sufficient to cause severe disease (64). Additionally, sex hormones estradiol and progesterone are known to significantly affect immune responses to influenza (66, 67). Thus, it is imperative to understand the impact of pregnancy-associated changes on immune function in the context of influenza.

The role of altered cytokine and chemokine production, immune cell infiltration, and resultant tissue damage has been extensively studied in the context of influenza pathology (68–71). Due to several physiological changes, including elevated levels of estradiol and progesterone, cytokine concentration, as well as immune cell population, size and function are dramatically altered during pregnancy (72–74). Increased numbers of peripheral neutrophils, monocytes, and dendritic cells (DCs) are observed (74). However, NK cells and CD4 T cells produce smaller amounts of inflammatory cytokines and chemokines following *in vitro* stimulation (74). While these studies are helpful for our understanding of immunity during pregnancy, responses to influenza infection during pregnancy are still not very well characterized. Compared to postpartum and nonpregnant women, pregnant women exhibited lower circulating levels of IgG2 (antibody isotype correlated with protection) following infection during the 2009 H1N1 pandemic (75). Additionally, they also exhibited an attenuated innate interferon response, which may permit the presence of higher viral titers within the lung (76). Vaccination studies indicate that the adaptive immune responses in pregnant women are comparable to those of nonpregnant controls, evidenced by similar rates of seroconversion and seroprotection (77–79). However, one group demonstrated diminished induction of IgG1, IgG2, and IgG3 responses following vaccination with a pronounced effect during later stages of pregnancy (80).

These studies suggest that there is a paucity of data, specifically regarding the molecular mechanisms responsible for the altered immune responses to influenza infection observed during pregnancy. To address this, several animal studies have been conducted to provide insight into the mechanism of disease.

Pregnant mice infected with H1N1pdm09 experienced significantly higher mortality than nonpregnant females (75, 81). While some groups observed increased viral replication in the lungs of pregnant females, others suggest replication is unaffected by pregnancy (75, 81). Alternatively, a prominent association was observed between mortality and induction of proinflammatory cytokines and chemokines (TNF-α, CCL2, CCL3, and CXCL1) (75, 81). Increases in populations of pulmonary macrophages as well as Treg cells were observed, while CD8 T cells and neutralizing antibody titers were unaffected following infection (81). Pregnant mice have been shown to induce a robust antibody response following H1N1pdm09 infection (75); however, another study suggested a diminished response compared to that of nonpregnant mice (81). Thus, it appears that although profound changes were observed in the innate response to IAV infection, adaptive responses are much less affected.

The role of pregnancy-associated hormonal changes in mediating protection or increased severity of infection has also been explored (66, 67, 82). Elevation of estradiol (E2) has been shown to be protective in the context of both inactivated influenza vaccination as well as IAV infection in nonpregnant females (83). Another estrogen, estriol (E3), specifically induced in high quantities during pregnancy, has also been shown to confer protection following infection by reducing tissue inflammation (82). Similarly, progesterone treatment in nonpregnant females promoted accelerated recovery in influenza-infected females, possibly via the upregulation of the epidermal growth factor amphiregulin in lungs (84). Furthermore, reduced concentrations of progesterone in pregnant females correlated with increased severity and adverse fetal outcomes (85). Thus, it is unlikely that increased levels of E2, E3, and progesterone during pregnancy are responsible for severe disease. However, the impact of other estrogens (E1 and E4) and glucocorticoids, which are also altered during pregnancy, is unknown and requires further investigation. Limited studies have been conducted in

other models, such as guinea pigs, ferrets, and pigs, with no major differences in viral replication or morbidity between pregnant and nonpregnant females (50, 86–88).

It is evident across clinical and mouse data that pandemic influenza strains are more pathogenic in pregnant women than seasonal strains, reiterating the role of viral factors, such as antigenic shift, in the severity of disease (59–61, 89). However, there is also strong evidence indicating that the immunological shift, among other physiological changes observed during pregnancy, contributes to increased severity of influenza infection (58, 59, 64). Significant human and mouse literature suggests that this phenotype is a result of increased tissue damage within the respiratory tract due to the influx of inflammatory cells and the induction of proinflammatory cytokines and chemokines. However, there are major inconsistencies across studies with regard to the dynamics of specific cell populations, associated cytokines, and functions due to differences in strain of virus, dose of inoculum, mouse strain, and timing of infection. Some studies described an increase in cytokine induction (75, 81), whereas others reported an opposite phenotype following infection (90, 91). Several groups have demonstrated higher viral replication in pregnant mice than nonpregnant females (75, 81, 90, 92, 93), while one study reported no differences in viral replication (81).

Therefore, it is important to further systematically study the pathogenesis of IAV and associated immune responses in pregnant women as well as in animal models to improve our understanding and, thus, outcomes following infection. Studies accounting for host factors like pregnancy would also greatly help to develop more effective influenza vaccines for such high-risk populations.

ZIKV. Zika virus (ZIKV) is a single-stranded RNA virus in the family *Flaviviridae*. The transmission of ZIKV infection mostly commonly occurs through the bite of the *Aedes* mosquito. Furthermore, there are additional routes of ZIKV transmission: sexual, blood transfusion, and vertical transmission from mother to child (94–96). Clinical observation of birth defects during the recent epidemic emphasized ZIKV as an important threat to public health in 2015. The number of ZIKV disease cases reached 216,207 in Brazil, and 8,604 neonates were born with malformations (96–98).

Accumulating evidence suggests that primary human placental trophoblast cell lines, endothelial and Hoffbauer cells, are permissive to ZIKV infection and facilitate viral replication (99, 100). These observations highlight the potential role of the placenta as a reservoir and entry for the virus to reach the fetus, where ZIKV mostly infects neocortical neuroepithelial and neuronal stem cells (NSCs). In the NSCs, ZIKV induces apoptosis, reduced proliferation, and transcriptional alterations (101–103), which result in cortical alterations and neurodevelopmental anomalies (104).

The majority (50% to 80%) of ZIKV infections are asymptomatic. The most common signs and symptoms of ZIKV infection occur within a period of 3 to 14 days and last for up to 1 week and manifest as a rash, low-grade fever (72%), arthralgia and myalgia (65%), conjunctivitis (63%), headache (46%), fatigue, and/or rash (105–107). Complications are infrequent ($<$1%), but when they occur, they are severe and may be fatal: Guillain-Barre syndrome, transverse myelitis, iridocyclitis, maculopathy, thrombocytopenic purpura, and myocarditis (106). The manifestations of acute ZIKV infection are similar across age groups, in both sexes, and in pregnant women. ZIKV-infected mothers transmit ZIKV in 20 to 30% of cases to the fetus. Most fetuses and newborns are asymptomatic, but 4 to 7% of pregnancies exhibit miscarriage and 5 to 14% have congenital Zika syndrome (CZS; 4 to 6% microcephaly) (106).

CZS shares the symptoms and signs with other TORCH congenital infections, such as cognitive, sensory, and motor disabilities. However, there are signs that are unique to CZS: (i) severe microcephaly with partially collapsed skull; (ii) thin cerebral cortices with subcortical calcifications; (iii) macular scarring and focal pigmentary retinal mottling; (iv) congenital contractures; and (v) marked early hypertonia and symptoms of extrapyramidal involvement (94, 108). Furthermore, CZS can cause malformations of the important brain structures, such as the hippocampus, corpus callosum, basal ganglia, thalamus, cerebellum, and brainstem (109–112). The subcortical calcifications (as opposed to

periventricular in CMV) are observed when the infection occurs later in pregnancy and the brain is macroscopically well formed. CZS is also associated with intrauterine growth restriction, craniofacial malformations, and pulmonary hypoplasia (94).

The long-term development of infants with CZS most likely will be severely impacted. Sensorineural hearing impairment, hypertonia, spasticity dysphagia, and tremors are residual long-term manifestations of CZS (113, 114).

According to widely studied animal models of CZS, during Zika infection, the mother exhibits a systemic inflammatory response with increased IL-1β IL-2, IL-6, IL-7, IL-15, and IL-16. Furthermore, ZIKV infection leads to the inhibition of type I IFN production and downstream interferon-stimulated genes (ISGs) (115). ZIKV NS1, NS4A, and NS4B proteins function as the primary suppressors of type I IFN induction by blocking TBK1/IRF3 pathways. Multiple studies of the damaged fetal brain indicate significantly higher expression of NLRP1, NLRP3, and AIM2 and cytokines IL-1β, IL-6, IL-18, IL-33, and caspase 1 following ZIKV-induced inflammation (100, 115–118).

HIV. HIV-1 is a lentivirus that belongs to the family *Retroviridae*. Perinatally acquired HIV-1 infection is less common in the United States as a result of earlier identification of maternal HIV infection and comprehensive HIV antiretroviral treatment (3), reducing the perinatal transmission rate in the preantiretroviral era from 18% to 32% to 1% to 2% (3, 119). However, in resource-limited settings, such as sub-Saharan Africa, ~15 to 30% of infants become infected with HIV during pregnancy, with an additional 5 to 20% infected through breastfeeding (200,000 infants were infected in 2013) (1, 120).

The factors that increase the risk of perinatal HIV transmission are the maternal plasma viral load, maternal CD4 count, advanced WHO clinical disease stage, breastfeeding and mastitis, and acute maternal infection (3, 121, 122).

During maternal HIV-1 infection, maternal neutralizing antibodies (NAbs) and virions interact directly with placental macrophages (Hofbauer cells) prior to entering fetal circulation (123, 124). According to several studies, Hofbauer cells express HIV-1 (co)receptors CD4, CCR5, CXCR4, and DC-SIGN on their surface and sequester Abs and Ab-virion immune complexes, limiting HIV-1 mother-to-child transmission (MTCT) (123). Additional host restriction factors expressed by HCs or trophoblasts have been identified, including APOBEC3G and ISGs (124). Despite multiple studies, the strategy of HIV-1 evasion of the placenta and its transmission are poorly understood.

Several studies have confirmed the relationship of HIV seropositivity with increased risk of spontaneous abortion, stillbirth, intrauterine growth retardation, low birth weight, preterm birth (125–129), and neurodevelopmental delay (130). HIV is also associated with an increased risk of chorioamnionitis and deciduitis, which may in part explain the elevated risk for preterm birth (131, 132).

It is important to mention that postnatal growth of the children of HIV-infected women is often delayed even without the occurrence of vertical transmission. Furthermore, HIV-exposed uninfected infants (HEU) suffer from up to 4-fold higher rates of morbidity and mortality from diarrheal and respiratory illnesses than unexposed children (133–136). The pathophysiology of such increased risk of illness and death in HEU infants is multifactorial and can be related to the severity of maternal HIV disease (137), poor placental transfer of protective maternal antibodies (138, 139), replacement feeding rather than breast feeding (140), perinatal exposure to antiretroviral drugs (141–143), and increased exposure to pathogens from immunodeficient individuals in the household (144, 145).

Acute HIV infection results in the production of proinflammatory cytokines and chemokines, which help to recruit inflammatory cells to the site of infection. Phagocytes (neutrophils, monocytes/macrophages, and DCs) and other innate immune cells (such as plasma cell-like DCs that produce IFN and NK cells) are initially recruited to eliminate the infecting virus (146, 147). Early studies (147, 148) proved that neopterin and β2-microglobulin were increased in HIV infection. Elevated levels of IP-10 (also called CXCL10, a CXC chemokine) were associated with low CD4 counts, strongly indicating this marker as a predictor of HIV infection progression.

Following infection, DCs present antigen to T cells and B cells within lymphoid tissues to trigger the adaptive immune response. The major immune cells and associated cellular mediators in HIV-1 infection include (i) dendritic cells (cDC and pDC), macrophages, and NK cells (IFN-γ, IFN-α, IL-6, IL-7, IL-10, IL-12, IL-15, IL-18, IP-10, MCP-1, and TNF-α) and (ii) $CD4^+$ T cells (Th1, Th17, Treg, and Tfh), $CD8^+$ T cells, and B cells (IFN-γ, IL-7, IL-12, IL-15, IP-10, MIP-1β, RANTES, and A-SAA) (147).

Significant elevation of plasma CXCL13 levels during early and chronic HIV infection represents a novel marker of systemic immune activation during early and chronic HIV infection and may be used to predict the development of non-AIDS events.

One study (149) demonstrated that maternal HIV infection induces a state of fetal hyperferritinemia, which is unrelated to maternal ferritin level and does not appear to be secondary to the fetal proinflammatory state. Another study (150) demonstrated that women infected with HIV have an increased risk of malaria in pregnancy (MiP). MiP also was associated with increased sTNFR2, sICAM-1, and IL-18BP concentrations during pregnancy. Pregnant women who delivered preterm had increased concentrations of sTNFR2 and altered levels of IL-6. Interestingly, pregnant women with sTNFR2 concentrations in the highest quartile within 6 weeks of delivery had an elevated relative risk of preterm birth.

One study (151) of Brazilian mother-infant pairs found that levels of inflammation, monocyte activation, and oxidized low-density lipoprotein in HIV-exposed infants are higher than levels in unexposed infants at birth, some of which remain elevated for up to 6 months of life. Interestingly, the levels of these inflammatory markers were not related to maternal inflammatory status. Inflammation may contribute to the increased HIV-exposed, uninfected infectious morbidity and slow growth. In addition, the lack of correlation between maternal and neonatal inflammatory markers suggests that these biomarkers do not cross the placenta during HIV infection (152).

In summary, further research is required to determine the contribution of maternal and fetal immune responses to adverse outcomes among HIV-infected mothers and infants. Furthermore, advances in this area could aid in the development of novel therapeutic strategies targeting pathological inflammation in HIV-infected mothers and infants.

HCV. The worldwide prevalence of hepatitis C virus (HCV) infection is between 1% and 8% in pregnant women and between 0.05% and 5% in children (153). MTCT is the main cause of HCV infection in children, with an incidence from 3% to 10% (154) and a 2- to 4-fold increase upon coinfection with HIV-1 (155, 156). HCV may directly impact maternal health during pregnancy or influence pregnancy outcomes due to MTCT or maternal infection. Chronic HCV itself does not seem to have a negative effect on pregnancy, while there are few related pathological studies.

Serum alanine aminotransferase (ALT) levels were observed to be elevated in nonpregnant individuals infected with HCV as a result of leakage from the liver due to immune-mediated damage of parenchymal liver cells. However, recent studies found that in pregnant women with hepatitis C, maternal serum ALT levels decrease during the first trimester of pregnancy and rise after delivery, while HCV RNA levels increase during the second and third trimesters (157, 158). This inconsistency between ALT levels of pregnant and nonpregnant individuals might be due to maternal-fetal tolerance mechanisms that induce an inhibitory effect on cellular immunity to suppress HCV-specific cytotoxic T-lymphocyte (CTL) activity, thereby preventing hepatocyte destruction (159). Additionally, the placenta also releases endogenous IFN-α during pregnancy, which can influence ALT levels; however, its effect on viral clearance is unclear (160).

Research found that HCV coinfection was significantly associated with cholestasis (161, 162). HCV infection during pregnancy may increase the risk of adverse perinatal outcomes, such as preterm delivery, FGR, congenital malformations, and overall perinatal mortality (163–166). However, there is a lack of consistency between reports of

maternal and fetal morbidity and outcome across different studies, primarily due to small sample sizes.

There is about a 5% risk of transmission of the virus from mother to baby. HCV may pass from mother to child during pregnancy and childbirth, while breastfeeding does not appear to contribute to an increase in HCV transmission rate (167, 168). Furthermore, the mode of delivery, vaginal or cesarean section, did not show differences in rates of HCV vertical transmission (169).

HCV may be transmitted to infant blood through maternal blood leakage or through placenta, but the underlying molecular mechanisms are unclear. Studies have indicated the ability of HCV to infect placental cytotrophoblasts *in vitro* (170). Additionally, peripheral blood mononuclear cell (PBMC) infection was demonstrated to be a critical risk factor for perinatal transmission of HCV. PBMCs can act as a vector of the virus and transfer it to the target cells of a new host or produce foreign bodies containing HCV, which can enter the fetal bloodstream independently and cause vertical transmission (171).

Research found that newborns exposed to HCV have activation of inhibitory T cells and proinflammatory markers, which are offset by higher IFN-γ production (172). This suggests a balance between proinflammatory and anti-inflammatory responses in newborns exposed to HCV, which may be responsible for prevention of HCV infection *in utero*.

Anti-HCV antibodies (anti-HCV Ab) can be transmitted across the placenta from a pregnant woman to the fetus, and neonatal serum can be detected as anti-HCV positive up to 13 months after birth. The American Academy of Pediatrics and the U.S. Centers for Disease Control and Prevention (CDC) recommend anti-HCV screening for babies born to HCV-positive women after 18 months or HCV RNA screening for 1-month-old babies twice (173). Ribavirin is banned during pregnancy because of its known teratogenicity. In addition, after discontinuation of ribavirin, the risk of teratogenesis persists for up to 6 months and applies to women taking ribavirin and male and female partners taking ribavirin.

It has been found that human trophoblast cells infected with HCV-RNA can induce strong upregulation of type I/III IFN and increased expression of chemokines such as CCL5 (RANTES), CXCL10 (IP-10), and CXCL11 (I-TAC), inducing the recruitment and activation of decidual NK cells (1). At the same time, it was observed that HCV-RNA transfection could induce apoptosis in HTR8 cells, which may affect the morphology of placenta.

The difference between ALT and HCV^- RNA observed in postpartum HCV^- RNA^+ women may be due to the different proportions of Th1 cytokines produced (2). A study of mothers and infants infected with HCV examined umbilical cord blood, placenta, and decidua by isolating mononuclear cells. This study found that the gradient of the proportion frequency of NKT and γ δ-T cells in placenta was higher than that in umbilical cord blood. HCV infection can enhance the cytotoxicity of NK and NKT cells in placenta (3). The polymorphisms of the IL-28B promoter, mannose-binding lectin, TNF-α, IFN-γ, IL-10, and TGF-β have also been used to study the risk of mother-to-child transmission of HCV (4, 5).

In the case of uncontrolled replication, infected hepatocytes secrete cytokines, such as IL-8, CXCL-9, and CXCL-10, to recruit T cells to the infected liver, all of which are associated with previous damage (174, 175). During HCV infection, TNF-α is considered the key molecule to promote insulin resistance and diabetes. The ratio of TNF-α to interleukin-10 is higher in patients with severe liver disease and liver cancer (176, 177). Liver TNF-α is associated with increased inflammatory activity, liver fibrosis, and liver injury in patients with chronic hepatitis C (178, 179). In patients with mixed infection of HCV and HBV, the concentration of IL-6 was positively correlated with the course of disease and viral load, while the concentration of IL-18 was positively correlated with the levels of ALT and aspartate transaminase, and the effect of interferon on immune status could be evaluated (180).

The researchers found that serum mediators such as IL-6, IL-8, CXCL-9, CXCL-10, CXCL-12, and macrophage migration inhibitory factor (MIF) can be used as potential markers to evaluate the progression of chronic hepatitis to liver cirrhosis (181, 182).

RV. Rubella virus (RV), also called German measles or 3-day measles, is a member of the family *Togaviridae*, genus *Rubivirus*. Humans are the only known reservoir for rubella infection. The proportion of women of childbearing age who are susceptible to rubella varies greatly among nations, where infection rates are negatively correlated with vaccine coverage.

Maternal acquired rubella is usually a mild, self-limited disease. Erythematous maculopapular eruption as well as prodromal symptoms, such as low fever, conjunctivitis, rhinitis, sore throat, and cough, are observed. Polyarthritis and polyarthralgia are potential sequelae. However, in spite of the mother being asymptomatic or having mild symptoms, rubella infection can have devastating effects for the developing fetus during pregnancy.

Clinical outcomes of maternal infection with rubella are dependent on gestational age. Risk to the fetus is highest during the first trimester and reduces with gestational age. Infection during pregnancy can result in stillbirths, spontaneous abortion, or several anomalies associated with congenital rubella syndrome (CRS). This syndrome can cause one or more problems to infants, such as growth delays, cataracts, glaucoma, deafness, congenital heart defects, defects in other organs, and intellectual disabilities (183).

The pathogenesis of congenital rubella is not completely understood. The virus enters the fetus via the maternal bloodstream and infects the epithelium of chorionic villi and the endothelium of the blood vessels of the placenta (184). Pathological evidence suggests that rubella virus spreads through the vascular system of the developing fetus after infecting the placenta and results in defects due to cytopathic effects within fetal organs (185, 186). RV induces apoptosis in monolayers of human normal-term placental chorionic explants (CVE) and cytotrophoblasts (CTB) but does not induce apoptosis in human fetal fibroblast (HEF) culture of primary human embryonic fibroblasts (187, 188). RV replication in the host cells can directly or indirectly affect the expression of genes involved in the development of sensory organs (189). The lifelong effect of RV on developing fetus is cumulative, which is related to the interaction of host with RV protein (189). The replication cycle of RV was longer, and the replication dynamics was slower (190).

Inflammatory chemokines were observed to be increased in the supernatant of RV-infected endothelial cells (191). The level of IFNs induced by the RV strain in placenta was significantly different, but there was no significant difference in lung or leukocyte culture (192). The cellular immunity of 738 pupils vaccinated with RV vaccine has shifted to the proinflammatory cytokine spectrum, in which the levels of IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), and TNF-α are increased while the detection rate of IL-10 is the lowest (193).

SARS-CoV-2. In December 2019, a novel type of coronavirus was identified in patients with infectious respiratory disease in Wuhan, China, with the ability of human-to-human transmission. The disease, termed coronavirus disease 2019 (COVID-19), has expanded globally exceptionally swiftly. COVID-19 is caused by the virus severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), a novel enveloped RNA beta-coronavirus. The primary phenotype of COVID-19 is severe acute respiratory distress syndrome (ARDS). With the spread of this novel coronavirus, interests have expanded to the role of the virus in pregnancy, including potential intrauterine transmission from mother to fetus as well as maternal and fetal outcomes in pregnant women infected with SARS-CoV-2.

In a systematic review including 356 cases (33 studies) in pregnant women, the most frequent symptoms were fever (67%), cough (66%), dyspnea (7%), sore throat (7%), fatigue (7%), and myalgia (6%) (194). Rhinorrhea/nasal congestion, anorexia, nausea/vomiting, headache, and possible abnormalities in smell and/or taste have also been

reported. Laboratory findings included lymphopenia (14%), mild increase in liver enzymes (5%), and thrombocytopenia (1%). These clinical manifestations are similar to those in nonpregnant individuals reported in a 138-case cohort study (195).

Some data showed that pregnancy and childbirth do not increase the risk of contracting SARS-CoV-2 and do not worsen the clinical course of COVID-19 compared with those of age-matched nonpregnant patients (196–199). The majority of pregnant women who develop severe COVID-19 are younger (200), while within the general population, those affected by severe disease are older (201). Pregnant patients with severe disease also may suffer from other comorbidities that may increase or exacerbate the risk of severe disease (such as hypertension, diabetes, severe obesity, severe asthma, serious heart disease, and immunocompromise) (202).

Some studies (203, 204) reported that patients with severe COVID-19 have laboratory evidence of a cytokine storm-related syndrome induced by a strong inflammatory response, which has been proven to cause severe and fatal illnesses. However, whether the normal alterations within the immune system during pregnancy can influence the course of this response remains an open question.

A review analyzing 51 pregnant patients with confirmed COVID-19 reported that the preterm birth rate (delivered before 37 weeks of gestation) is 39%, where 96% were delivered by cesarean (198). A larger systematic review of 252 pregnant COVID-19 patients reported that the preterm birth rate is 15.2% when 69.4% were delivered by cesarean (194). The frequency of spontaneous abortion (0.8%) (194) is not increased, per current data (194, 205). However, there are limited data available for pregnant patients who were infected during the first trimester. Two reports (206, 207) described two critically ill women who had fetal deaths, where one of the two women died while the other was treated with extracorporeal membrane oxygenation.

For neonatal outcomes, among 256 newborns from one review (194), more than 95% of newborns were healthy at birth. Neonatal complications have been linked mainly to preterm birth (194). Specifically, preterm birth ($<$37 weeks of gestation) occurred in 39 (15.2%) newborns. Birthweight ranged from 1,520 to 4,050 g, among which a low birth weight ($<$2,500 g) was reported in 20 (7.8%) newborns, while intrauterine fetal distress was observed in 20 (7.8%) newborns. In addition, 3.1% were admitted to the neonatal intensive care unit, 1.2% were put on neonatal mechanical ventilation, 4.7% had respiratory distress syndrome, 1.2% had neonatal pneumonia (3 cases), and 1.2% had disseminated intravascular coagulation. Mortality occurred in 3 cases.

Four (1.6%) newborns, delivered by cesarean section, had a positive reverse transcription PCR test result, while samples from their cord blood, placenta, and amniotic fluid were negative (194). Three (1.2%) newborns had positive IgM, and 6 (2.3%) had a positive IgG test. PCR test for COVID-19 in samples from 30 cord blood, 23 amniotic fluid, and 12 placenta specimens were all negative. All samples of breast milk from 26 women tested negative for COVID-19 (194).

In addition, hyperthermia is the most common clinical manifestation in pregnant women with COVID-19, as mentioned above. Considering this, a theoretical concern should be focused on the fact that high maternal core temperature from a febrile illness such as COVID-19 during organogenesis in the first trimester may be associated with an increased risk of congenital anomalies, especially neural tube defects, or miscarriage. However, the incidence of these outcomes has not been observed. Longitudinal monitoring of the neonates born to infected mothers would provide further insight into subtle consequences of maternal infection during pregnancy.

There is a hypothetical opportunity of vertical transmission, similar to that seen in SARS, as the aminopeptidase-angiotensin-converting enzyme 2 (ACE2) receptor is generally expressed in the placenta (208) and a similar receptor-binding domain between SARS-CoV and SARS-CoV-2 (209). However, maternal viremia rates appear to be low (1% in one study [210]), indicating that placental seeding and vertical transmission are highly unlikely. Besides, no confirmed cases of intrauterine transmission have been reported in reviews including 51 pregnant women with COVID-19 (197, 198,

211). In addition, several suspected cases based on newborn laboratory and/or clinical findings have been reported (212–215), but SARS-CoV-2 testing on fetal blood, amniotic fluid, and placenta was either negative or not performed. The majority of these infants were delivered by cesarean and had positive nasopharyngeal cultures for SARS-CoV-2 on day 1 or 2 of life, an increased IgM level, and/or pneumonia. Positive IgM results are not definitive evidence of *in utero* infection, and, in most of these cases, early infant infection may have been due to close contact with infected parents or caregivers (216).

Based on the current data available, there have been no confirmed cases of vertical transmission among the neonates born to COVID-19-infected mothers reported. However, it is important to note that the majority of the mothers acquired COVID-19 in the third trimester, and there are limited data for infection earlier in pregnancy.

In pregnant and nonpregnant patients, the main phenotype of COVID-19 is ARDS, a potentially lethal syndrome caused by pneumonia, sepsis, or aspiration due to cytokine storms (217). This occurs following viral entry into alveolar epithelial cells via the membrane-bound ACE2 receptor. This results in the activation of the innate immune and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6, IL-2, IL-7, IL-10, TNF-α, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein 1 alpha (MIP1A), monocyte chemoattractant protein (MCP1), and interferon-γ-inducible protein (IP10), inducing a cytokine storm (209, 217–219).

Interestingly, patients with COVID-19 reveal the activation of both Th1 and Th2 immunity, culminating in the presence of IFN-γ and IL-1β as well as IL-4 and IL-10 (203). Furthermore, elevated levels of IL-6 (a predominantly Th1 response) are associated with a significantly increased risk of mortality in COVID-19 patients (220). Based on this observation, tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), has been experimentally applied for the treatment of critical COVID-19 pneumonia in China and Italy with promising results.

In pregnancy, there is an attenuation in Th1 cell-mediated immunity due to the physiological transition to a Th2-dominant environment. In addition, changes of the hormonal milieu in pregnancy would influence immunological responses to viral pathogens. Th2-dominant environment and hormonal milieu tend to increase the expression of anti-inflammatory cytokines (IL-4 and IL-10) and other unidentified immune adaptations, which may be responsible for the predominant immune response to SARS-CoV-2, resulting in the lesser severity of COVID-19 than that in nonpregnant patients (221).

One study reported (222) that SARS-CoV-2 might attack hemoglobin, causing critically low oxygen saturation. According to this theory, the fetus may receive less oxygen due to reduced maternal hemoglobin. The placenta has the role of exchanging carbon dioxide and oxygen between mother and fetus. Therefore, COVID-19 attacking hemoglobin would produce iron, carbon dioxide, and oxygen, which might induce toxicity in placental and fetal cells. In addition, capillaries would be easily broken due to inflammation. Proteins such as fibrinogen fill the capillaries' cracks via the coagulation reaction, which will also lead to severe placental inflammation.

CONCLUSIONS AND FUTURE DIRECTIONS

Perinatal outcomes from viral infections during pregnancy can range from mild to asymptomatic disease to pregnancy loss by spontaneous abortion as well as fetal infection, resulting in congenital viral syndromes. Prenatal care has no true standards for antenatal management for most viral infections during pregnancy, with no available standardized treatment or preventative strategies.

Most viral infections during pregnancy interfere with IFN and TNF signaling, but, due to diverse antigenic properties, they exhibit different tissue tropism and outcomes. CMV interferes with TLR-2 responses and is neurotropic, resulting in congenital fetal anomalies. HSV and VZV are also neurotropic, while VZV additionally induces TGF-β, IL-1α, IL-6, and CXCL10 production. Influenza virus causes IL-1α, IL-6, CXCL10, and TGF-β elevation and has a more pronounced effect on the mother than the fetus. In

contrast, ZIKV is neurotropic and causes fetal brain damage by inhibiting type I IFN responses and inducing IL-1β, IL-6, IL-18, NLRP1, NLRP3, and AIM2 expression. Rubella, similarly, can cause congenital rubella syndrome in the fetus and has endothelial and neural tropism, inducing IL-6, GM-CSF, and TNF-α. In addition, we reviewed other viruses, such as HIV and HCV, which do not cause severe congenital anomalies but are of interest because of possible transmission to the fetus. Lastly, SARS-CoV2, which is currently highly clinically relevant due to the large number of cases during the pandemic, is tropic to the ACE2 receptor in the lung tissues and causes IL-6 and IFN-γ activation. Importantly, pregnancy and childbirth do not exacerbate the risk of acquiring SARS-CoV-2 or severe disease and do not result in worse pregnancy outcomes.

There is a dearth of information with regard to viral pathogenesis and inflammation during pregnancy. Several studies are required to investigate the diverse mechanisms employed by viruses to induce disease in pregnant women as well as the complex, potentially pathological immune responses induced in response to infection. Further insight into specific molecular mechanisms responsible for the increased severity of disease in mothers and/or neonates due to viral infections and associated inflammation would be greatly beneficial in improving clinical care during pregnancy. Additionally, this knowledge could aid in efforts to develop novel therapeutics targeting uncontrolled inflammatory responses to viral infection during pregnancy to prevent adverse fetal outcomes.

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