SPECIAL ISSUE ARTICLE

COVID-19 in pregnancy: Placental and neonatal involvement

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Abstract

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 12 million infections and more than 550 000 deaths.[1] Morbidity and mortality appear partly due to host inflammatory response.[2] Despite rapid, global research, the effect of SARS-CoV-2 on the developing fetus remains unclear. Case reports indicate that vertical transmission is uncommon; however, there is evidence that placental and fetal infection can occur.[3-7] Placentas from infected patients show inflammatory, thrombotic, and vascular changes that have been found in other inflammatory conditions.[8,9] This suggests that the inflammatory nature of SARS-CoV-2 infection during pregnancy could cause adverse obstetric and neonatal events. Exposure to intrauterine inflammation and placental changes could also potentially result in long-term, multisystemic defects in exposed infants. This review will summarize the known literature on the placenta in SARS-CoV-2 infection, evidence of vertical transmission, and possible outcomes of prenatal exposure to the virus.

KEYWORDS
COVID-19, intrauterine infection, neonates, pathology, placenta, pregnancy

1 | INTRODUCTION

The first cases of severe pneumonia from a novel coronavirus were reported in Wuhan, China in December 2019.[10] Since then, the virus has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection causes fevers, cough, dyspnea, myalgias, pharyngitis, diarrhea, pneumonia, acute respiratory distress syndrome, multisystem organ failure, cytokine storm, endothelial damage, and thrombotic events.[2,3,11-13] It has infected over 12 million people and caused over 550 000 deaths across the globe.[1] The case fatality rate is estimated at 2.3% among the entire population.[14] Recent observations show that the majority of pregnant women are asymptomatic or have mild disease based on the criteria proposed by Wu et al.[14-16] Nevertheless, any infection during pregnancy has potential risks. A recent review of obstetric cases found that 3% of pregnant women with SARS-CoV-2 required intensive care.[17] There have also been cases of preterm labor and perinatal death in the setting of maternal SARS-CoV-2 infection. It is uncertain whether the virus can be vertically transmitted from mother to neonate. Given that SARS-CoV-2 causes inflammatory, coagulation, and endothelial changes, investigating placental and fetal involvement during infection is crucial to providing guidance and care to pregnant patients.

Coronaviruses are enveloped positive-sense single-stranded RNA viruses that infect both humans and animals.[18] Human coronaviruses typically cause mild upper and lower respiratory infections, although they can present as severe pneumonia or bronchiolitis.[7,18] Gastrointestinal symptoms can also occur with infection. Coronaviruses were believed to have little clinical significance until the 21st century. Since 2002, three novel coronaviruses have been described: SARS-CoV in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019. SARS-CoV appears to primarily target ciliated epithelial cells via the angiotension-converting enzyme 2 (ACE2) receptor. ACE2 is expressed in the cardiovascular system, gut tissue, adipose tissue, lungs, kidneys, the placenta, and fetal tissue.[19-21] SARS-CoV-2 also binds to ACE2 in order to enter cells.[19,20,22] The clinical presentation of coronaviruses is likely due to both direct cell injury and host response.

Human coronavirus infections are associated with an increase in interferon (IFN)-γ and interleukin (IL)-8.[18] SARS-CoV and MERS-CoV infections increase T-helper (Th)1 cell-associated proinflammatory cytokines: IL-1β, IL-6, and tumor necrosis factor (TNF).[2] These infections also cause delayed, decreased antiviral IFN activity. SARS-CoV-2 infection presents with similar proinflammatory changes as SARS-CoV and MERS-CoV infections. Increased Th2 cell-associated cytokines are found in SARS-CoV-2 infections as well.[2,11] There is widespread interest and research in developing a SARS-CoV-2 vaccine; however, prior studies indicate that long-term immunity may not be achievable. In human trials, immunoglobulins IgG and IgA increased about 2 weeks after infection with human coronaviruses; however, these antibodies quickly declined.[18] Individuals who have been previously infected with human coronaviruses have little to no protection against reinfection in the subsequent season.

Maternal-fetal immunity is a rapidly expanding field of research. Our knowledge of the placenta as an immune organ has progressed significantly over recent years. The placenta is composed of fetal trophoblasts and decidua derived from maternal endometrium.[22,23] Trophoblasts form floating and anchoring villi that interact with the decidua and the intervillous space, respectively. Multinucleated syncytiotrophoblasts (SYN) compose the outermost layer of the villi, which comes into direct contact with maternal blood. Mononuclear cytotrophoblasts comprise the inner layer of villi. The placenta has several mechanisms to prevent transmission of viral infections to the fetus.[24] As part of the innate immune system, the SYN is a physical barrier to infections.[25] Recent research has shown that trophoblasts induce autophagy during viral infection and can also induce resistance to viruses in neighboring cells.[26,27] The SYN contain neonatal FcRN receptors that transport maternal IgG to the fetus, thereby conferring humoral immunity.[28]

Viral infections during pregnancy have a broad spectrum of placental and neonatal pathology. Numerous viruses cause villitis and spontaneous abortion.[29-31] Congenital viral infections in the neonate can result in lifelong disabilities, sepsis, multisystem organ damage, and death.[32] Vertical transmission of viruses during pregnancy is incompletely defined.[24,31] Potential mechanisms of fetal infection include contact between maternal endothelium and cytotrophoblasts, infected maternal macrophages, ascending urogenital infections, and spread from maternal bloodstream to fetal capillaries. Finally, maternal infections can be transmitted to the neonate during labor.[33]

2 | REVIEW Of SARS-CoV AND MERS-CoV

In November 2002, the first death from SARS-CoV occurred. SARS-CoV is believed to have originated in bats. It was then transmitted to palm civets, and subsequently humans.[34] SARS-CoV presents with a flu-like illness and severe pneumonia. Complications during pregnancy include maternal death, hypoxia, disseminated intravascular coagulopathy, intrauterine fetal demise, intrauterine growth restriction, preterm delivery, and spontaneous abortion.[35] Ng et al described placental pathology from seven cases of SARS-CoV

infection during pregnancy.[36] Placentas delivered from women who had recovered from SARS-CoV during the first trimester had normal pathology. Placentas delivered from women who had active SARS-CoV infection showed increased intervillous and subchorionic fibrin, which the authors attributed to maternal hypoxia. Placentas delivered from two women who had recovered from SARS-CoV during the third trimester had extensive fetal thrombotic vasculopathy and areas of avascular fibrotic villi. The associated neonates both had intrauterine growth restriction. The authors postulated that placental hypoxia or increased thrombotic activity could have caused these pathologic findings. There have been no cases of vertical transmission during SARS-CoV infection.[35]

Middle East respiratory syndrome coronavirus emerged in June 2012 on the Arabian Peninsula.[37] Similar to SARS-CoV, MERS-CoV infects the lower respiratory tract, causing severe pneumonia. Current research indicates that bats infected dromedary camels with MERS-CoV about 30 years ago. Camels then transmitted the virus to humans. There have been only 11 cases of MERS-CoV infection during pregnancy to date.[38] The majority of MERS-CoV infections during pregnancy resulted in adverse outcomes ranging from preterm labor to maternal and fetal death. The case fatality rate of MERS-CoV infection is similar in pregnant women as in non-pregnant patients. Vertical transmission of MERS-CoV has not been reported.[35] Literature search revealed no case series of placental pathology from MERS-CoV–positive patients; however Jeong et al described a South Korean patient who was diagnosed with MERS-CoV at 35 weeks and 4 days gestation.[39] Fifteen days after diagnosis, she had clinically recovered from MERS-CoV, but developed a 10% placental abruption. The authors did not note any additional placental abnormalities. Given the high morbidity and mortality of MERS-CoV infection in pregnancy, it is likely that infection causes similar placental changes as those found in SARS-CoV infections.

3 | REVIEW OF SARS-CoV-2

At this time, it is unclear whether SARS-CoV-2 can be vertically transmitted. The majority of case reports of SARS-CoV-2–positive pregnancies document negative polymerase chain reaction (PCR) results for SARS-CoV-2 in the neonate, placenta, cord blood, and vaginal secretions.[3,8,40-44] The majority of neonates in these cases had uneventful hospitalizations. However, there are cases of neonates who have tested positive for SARS-CoV-2 after delivery,[5,6] as well as a few neonates who have had positive IgM antibodies to SARS-CoV-2.[4,45] IgM does not cross the placenta. SARS-CoV-2 IgM can appear as early as a few days after infection but peaks around 2 weeks.[46,47] Therefore, the presence of IgM in a neonate after delivery could indicate congenital infection.

There are also reports of placental SARS-CoV-2 infection. In a case report from Switzerland, a 26-year-old woman with SARS-CoV-2 infection had preterm labor and fetal demise at 19 weeks of gestation.[7] Fetal tissue was negative for SARS-CoV-2; however, PCR of the fetal surface of the placenta was positive. Pathology of

the placenta was notable for areas of inflammation, increased fibrin deposition, and funisitis. PCR of maternal blood, vaginal secretions, and urine were negative for SARS-CoV-2. Similarly, a case report from Italy describes two SARS-CoV-2–positive neonates born to SARS-CoV-2–positive mothers.[5] PCR of the placentas was positive for SARS-CoV-2, and in situ hybridization visualized SARS-CoV-2 spike proteins in the SYN layer of both specimens. Pathology was notable for chronic intervillositis. In this case series, one neonate was delivered at 35 1/7 weeks for non-reassuring fetal heart tones and required routine preterm care. Kirtsman et al reported a case of SARS-CoV-2 infection in a Canadian woman. She required urgent cesarean section for coagulopathy at 35 5/7 weeks of gestation.[6] PCR of maternal and fetal placenta, vaginal swab, breastmilk, neonatal blood, and neonatal nasopharynx were positive for SARS-CoV-2. All placental sections sampled had diffuse inflammation and early infarction. The neonate required a brief NICU admission for hypoglycemia and hypothermia. A preprinted case report from The Netherlands described an asymptomatic pregnant woman presenting with fetal distress.[48] SARS-CoV-2 PCR was positive on the maternal and fetal side of the placenta. In situ hybridization visualized SARS-CoV-2 particles in the SYN layer. The SYN also showed signs of damage and had inflammatory infiltrates. The neonate presented with multiorgan failure but had a negative SARS-CoV-2 PCR. In another preprinted case, a woman in the second trimester tested positive for SARS-CoV-2 in the setting of preeclampsia and placental abruption. The neonate was negative for SARS-CoV-2; however, SARS-CoV-2 virus was found in the SYN layer of the placenta.[49] These cases demonstrate that SARS-CoV-2 could infect the placenta. Only some reports describe neonatal SARS-CoV-2 infection in the setting of placental infection. These discrepancies could be due to rapid degradation of RNA after delivery. Alternatively, placental immune function could protect some neonates from SARS-CoV-2. Further observations and research are required to determine the potential mechanisms and prevention of SARS-CoV-2 vertical transmission.

As with SARS-CoV and MERS-CoV, SARS-CoV-2 infection causes inflammatory and vascular changes in the placenta (Table 1). A recently published study of 15 placentas from SARS-CoV-2 positive or convalescing mothers showed statistically significant increase in maternal vascular malperfusion (MVM) as compared to controls.[8] Pathological findings consistent with MVM included decidual arteriopathy, fibrinoid necrosis, and amniotic membrane arteriole hypertrophy. Placentas from SARS-CoV-2–positive women also had significantly increased intervillous thrombi. In a case series of 20 placentas from SARS-CoV-2 patients, fetal vascular malperfusion was the most common pathology found (9 cases).[9] Intramural, non-occlusive thrombi were also noted in several placentas. Villitis was found in four cases. One placenta had chorioamnionitis and funisitis, which was delivered from a woman with pneumonia and hypoxia. While neither study tested placentas for SARS-CoV-2 infection, all associated neonates were negative for SARS-CoV-2 on PCR. These reports demonstrate that SARS-CoV-2 infection can cause inflammatory and vascular changes of the placenta. Non-infectious inflammation causes similar placental endothelial damage and thrombi in mice.[50]

TABLE 1 Pathologic and infectious findings in placentas. Forty-five total cases are included (Baud et al, Chen et al, Shanes et al, Patanè et al, Kirstman et al, Baergen et al, Schoenmakers et al, Blauvelt et al, and Hosier et al). SARS-CoV-2 evaluation was not performed in Shanes et al, Baergen et al, and Blauvelt et al. SARS-CoV-2 results were positive in Hosier et al, but these were not included as methods were not available at time of publication.

Placental pathology or infection	Number of specimens
Maternal vascular malperfusion	17
Fetal vascular malperfusion	21
Inflammatory infiltrates	4
Increased fibrin	15
Thrombi	9
Villitis	6
Villous edema	5
Deciduitis	1
Intervillous inflammation	6
Infarction	1
Chorioamnionitis	3
Funisitis	3
Umbilical arteritis	1
SARS-CoV-2 PCR positive	5
In situ hybridization visualization	3

Alternatively, SARS-CoV-2 infection could cause hypercoagulability in the placenta as has been shown in other organs.[13] Regardless of mechanism, these placental changes could have deleterious effects on both mother and fetus. In the mouse model, endothelial and thrombotic alterations in the placenta are associated with altered vascular flow to the fetus and subsequent neural inflammation.[50] Therefore, children born to SARS-CoV-2 infected women could have similar neurologic inflammation prior to birth.

4 | DISCUSSION

It is difficult to interpret these cases due to our limited understanding of SARS-CoV-2 pathogenesis in the placenta and neonate. Serologic testing for SARS-CoV-2 is variable at this time.[51] Furthermore, the appropriate means of screening neonates has not yet been established. IgM cutoffs are based on adult data; however, neonates produce less immunoglobulins than adults.[33] Diagnosing congenital infections varies considerably between viruses. For example, IgG and IgM are not recommended for congenital cytomegalovirus diagnosis.[52] Rather, PCR of saliva and urine are the most sensitive and specific tests for this infection. If vertical transmission can occur during pregnancy, the clinical effects could vary with gestational age. Some cases of possible placental and neonatal SARS-CoV-2 infection were in the setting of preterm labor or fetal distress, suggesting that timing of maternal infection could affect the severity of presentation. Continued research and monitoring are required

to ensure that infants are being appropriately screened for SARS-CoV-2 infection after delivery. In the setting of this uncertainty, it appears that the vast majority of infants born to SARS-CoV-2–positive or convalescing mothers do not have viremia, congenital infection, or viral replication in the nasopharynx.

There are several cases of possible SARS-CoV-2 infection of the placenta and neonate. Li et al reported ACE2 receptors on fetal cardiovascular, lung, and liver tissue as well as in the decidua and cytotrophoblasts.[21] The presence of ACE2 receptors provides a plausible means for congenital infection. Notably, Kirstman et al described SARS-CoV-2 RNA in both neonate and placenta as well as elevated neonatal transaminases and neutropenia.[6] These lab abnormalities could be due to SARS-CoV-2 infection of the neonatal liver. Regardless of vertical transmission, maternal infection may cause other harmful effects on the neonate. For example, there is long-standing evidence that HIV exposed unaffected (HEU) infants have higher morbidity and mortality compared to peers.[53,54] There is a growing body of research that demonstrates that HEU infants have elevated inflammatory markers, decreased CD4 counts, and decreased humoral immunity. These changes have been attributed to maternal inflammation, viremia, and immunosuppression. SARS-CoV-2 is a highly proinflammatory infection that may cause similar changes in neonatal inflammation and immunity.

Although the majority of reports on SARS-CoV-2 in pregnant women, to date, note the presence of relatively mild symptoms among this population, symptomology may not reflect the severity of inflammation provoked by infection. Maternal inflammation has been implicated in a number of neonatal outcomes in addition to neonatal immunity. As mentioned above, coronaviruses have been shown to trigger pattern recognition receptors that lead to activation of transcriptional programs, which in turn induce a proinflammatory cytokine storm, largely driven by production of IL-6.[55] Both an inflammatory and prognostic marker, IL-6 can predict disease progression in adults, as noted in a United States cohort of pregnant patients with severe to critical SARS-CoV-2 infection.[56,57] In response to infection during pregnancy, maternal immune activation (MIA) and inflammation have been linked to a spectrum of adverse short- and long-term outcomes in infants.[58,59] Pregnancy itself represents a unique interplay of modulated immune states that vary by stage of gestation.[60] Host response to viral infection in pregnancy induces the production of proinflammatory cytokines, like IL-1β, IL-6, and TNFα, that activate the maternal immune system and can cross the placental barrier.[61-63] Thus, even in the absence of fetal viral infection or severe maternal symptoms, placental infection can trigger a fetal inflammatory response, leading to multiorgan system damage and predisposition for negative developmental consequences (Table 2).[64-70]

There is strong evidence to suggest that maternal inflammation associated with SARS-CoV-2 may confer long-term risk of neuropsychiatric disorders in children. MIA has been described as a "neurodevelopmental disease primer" that increases susceptibility of individuals to interacting genetic and environmental risk factors that can trigger neuro- or psychopathology later in life.[71] In particular, relationships between MIA and both autism spectrum disorder and schizophrenia have been well established through epidemiological and animal model studies,[72-75] whereas the effect of maternal infection and central nervous system (CNS) disorders like epilepsy and cerebral palsy have yet to be fully defined.[76,77] Research has also begun to suggest links between MIA and mood disorders, such as depression and bipolar affective disorder in children.[78,79] Proposed

TABLE 2 Pathology associated with inflammatory mechanisms in developing body systems of the infection-exposed neonate

Neonatal body system	Inflammatory mechanism	Pathology
Central nervous system (CNS)	Disruptions in neurotrophin signaling, activation of microglia, and potentiation of cell damage leading to abnormal cerebral development	Wide range of neuropsychiatric disorders and neurodevelopmental delay
Optic	Low serum insulin-like growth factor (IGF-1) during the course of maternal systemic inflammation and injury of developing blood vessels in retina	Retinopathy of prematurity
Pulmonary	Surfactant inactivation caused by inflammatory cytokine release and leakage of serum proteins into alveolar space	Surfactant deficiency and neonatal respiratory distress syndrome
Cardiac	Over-production of vasodilatory factors (nitric oxide, prostaglandin) that promote relaxation of the ductus	Patent ductus arteriosus
Renal	Activation of TLR-4 pathways and increased oxidative stress that induce glomerular and tubular damage	Neonatal hyperoxia-induced kidney injury
Adrenal	Cytokines alter programming of hypothalamic-pituitary-adrenal (HPA) axis	Elevated cortical levels with implications for long-term stress response
Gastrointestinal	Generation of inflammatory markers and reduction of intestinal innate immune cells impair intestinal development	Necrotizing enterocolitis
Immune	Activation of fetal innate immunity and T-cell pathways	Chronic inflammatory states (eg, atopic sensitization)
Multisystem	Ascending intra-amniotic infection induces an inflammatory cascade leading to spontaneous labor; mechanism of extrauterine infection is not well defined	Preterm labor and low birth weight

mechanisms include the stimulation of maternal cytokines and other inflammatory mediators that can cross the placenta and interfere with neurotrophin signaling, activate astrocytes and microglia, and potentiate cellular damage in the developing CNS of the fetus.[59] Such disruptions in neuronal cell differentiation can ultimately lead to abnormal fetal brain development.[80] Certain inflammatory markers, like C-reactive protein (CRP), an acute phase reactant, have been significantly associated with risk of selected neuropsychiatric disorders in children.[81,82] In a recent study from China, Wu et al reported higher mean serum levels of CRP in pregnant patients with SARS-CoV-2 infection compared to uninfected pregnant patients.[83] Beyond the question of vertical transmission, the long-term risk of neuropsychiatric disorders in children exposed to SARS-CoV-2 in utero warrants longitudinal investigation.

With regard to pregnancy complications of SARS-CoV-2 infection, several cases of fetal loss and preterm delivery due to fetal distress have been reported in SARS-CoV-2–positive pregnant women[5-7]; some larger studies and systematic reviews have also suggested that the rate of preterm birth in SARS-CoV-2 patients is higher than that of the general pregnant population.[84-86] As testing capacity increases and the burden of SARS-CoV-2 infection rises among the childbearing aged population, it is likely that even more preterm births will be reported among pregnant women with SARS-CoV-2 infection, compared to earlier reporting during the pandemic.[87] Existing literature provides substantial evidence to support an association between maternal viral infections and adverse pregnancy outcomes, including preterm labor and low birthweight.[58,88] It is estimated that intrauterine infection may account for up to 40% of premature deliveries.[89] Intra-amniotic infection induces an inflammatory cascade that leads to the initiation of spontaneous labor.[90-92] It is important to note that the described mechanism may occur with inflammation in the absence of infectious etiology.[88] Extrauterine infections, such as malaria, have also been associated with spontaneous preterm delivery, but specific mechanisms remain to be determined.[93] Preterm labor and low birth weight are leading global causes of neonatal and under-five mortality, as well as risk factors for poor developmental outcomes in children and adults later in life.[94] Preterm infants born to mothers with SARS-CoV-2 should be monitored closely for both short- and long-term complications.

Necrotizing enterocolitis (NEC) is one of the many risks of preterm birth. This inflammatory disease of the gastrointestinal tract is a significant cause of neonatal morbidity and mortality.[95-97] Both neonatal and maternal inflammation appear to contribute to NEC pathogenesis. In NEC, immature immune function and a highly immunoreactive preterm intestinal environment are hypothesized to produce a hyper-inflammatory response to microbial stimuli, characterized by exaggerated Toll-like Receptor (TLR)-4 signaling and decreased expression of IκB. IκB is an important regulator of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), a transcription factor that upregulates production of cytokines and immunological mediators.[98-100] In animal models, fetal exposure to maternal inflammation induced by chorioamnionitis has been shown to generate higher levels of inflammatory markers, like IL-6, and

reduced intestinal innate immune cells. This constellation of events impairs intestinal development and increases susceptibility to disorders like NEC.[101,102] Liu et al studied a cohort of 51 SARS-CoV-2–negative neonates born to infected mothers in the third trimester and observed a mean level of serum IL-6 (10.82 pg/mL) that was higher than the reference range (0.1-2.9 pg/mL).[103] One infant with extremely elevated IL-6 levels (as high as 109.42 pg/mL) developed NEC on day 22 after birth. High levels of inflammatory markers in SARS-CoV-2–exposed neonates likely reflect a process of maternal-fetal immune activation and should be interpreted as risk factors for diseases such as NEC.

Maternal immune activation and preterm birth pose an added short-term risk of bronchopulmonary dysplasia (BPD). Although existing literature supports an association between chorioamnionitis and decreased incidence of respiratory distress syndrome in preterm infants, prenatal inflammation has been further linked to fetal pulmonary injury that can progress to BPD.[104-106] In one prospective cohort of preterm infants, histological chorioamnionitis was associated with decreased efficacy of exogenous surfactant therapy.[107,108] This reduced efficacy is attributed to inactivation and increased clearance of surfactant, which could be due to leakage of serum proteins into the alveolar space and inflammatory cytokine release.[109] A few cases of SARS-CoV-2–exposed neonates had respiratory distress.[40,42] These presentations could be due to retained amniotic fluid or late prematurity. Alternatively, they could represent early lung damage in the setting of maternal inflammation. Longitudinal observations of long-term pulmonary sequelae in SARS-CoV-2–exposed infants are necessary.

In the present review, we have discussed the pregnancy outcomes of SARS-CoV and MERS-CoV infections and summarized available literature on placental inflammatory and thrombotic changes in SARS-CoV-2. At this time, it is uncertain whether SARS-CoV-2 can be vertically transmitted. Case reports indicate that placental and neonatal infection could occur and that maternal infection is associated with placental changes. Abundant scientific evidence demonstrates that maternal inflammation can cause a spectrum of lifelong sequelae in the offspring. Therefore, it is reasonable to speculate that the proinflammatory state of SARS-CoV-2 infection during pregnancy may precipitate negative consequences in children. In addition to potential risk of vertical transmission, SARS-CoV-2 may indirectly lead to adverse perinatal and long-term neurodevelopmental outcomes through MIA. Further investigation of inflammatory dysregulation in pregnant women with SARS-CoV-2 and longitudinal studies of developmental outcomes in SARS-CoV-2–exposed children are needed to ensure appropriate care of these growing populations.

CONFLICT OF INTEREST

The authors report no potential conflicts of interest.

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