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EDITORIAL COMMENTARY

# Severe Acute Respiratory Syndrome-Coronavirus-2 Effects at the Maternal-Fetal Interface

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**(See the Brief Reports by Guan et al, on pages 748–53 and Shook et al, on pages 754–8; See the Major Article by Regan et al, on pages 759–67.)**

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To the Editor—In this issue of *The Journal of Infectious Diseases*, 2 groups of investigators add to the body of literature cataloguing the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the pregnant host, including detailed histopathologic analysis of placentas resulting from pregnancies affected by SARS-CoV-2 infection resulting in intrauterine fetal demise (IUFD), as well as preterm labor [1, 2]. Early in the pandemic, it was documented that up to 15% of women screened during labor and delivery were found to be SARS-CoV-2 positive, the vast majority of whom were asymptomatic and unaware of infection [3]. It is likely that this rate of infection is even higher with more recently circulating and more contagious Delta and Omicron SARS-CoV-2 variants. Although many pregnant infected women remain asymptomatic, pregnant women or those who were recently pregnant are at increased risk for severe illness. This includes higher risk of hospitalization (31.5% vs 5.8% of nonpregnant women; risk ratio, 5.4), higher risk of intensive care unit level care requirement (adjusted risk ratio, 1.5), and higher risk of mechanical ventilation (adjusted risk ratio, 1.7) [4]. The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) documented that during the period from 1 March to 22 August 2020, approximately 25% of all women aged 15–49 years hospitalized with coronavirus disease 2019 (COVID-19) were pregnant. Of the 50% who were symptomatic, 16.2% were admitted to an intensive care unit and 8.5% required invasive mechanical ventilation [5].

Live-born infants born to infected mothers have a low incidence of infection and initial complications; however, as has been documented in the setting of other congenital and perinatally acquired infections, the effects of viral infection of the mother and ensuing inflammatory and vascular responses in the placenta may extend beyond direct viral infection of the fetus, by affecting the maternal-fetal interface and milieu during critical periods of development. The increasing catalogue of resultant detrimental effects of SARS-CoV-2 infection during pregnancy have included miscarriage, preterm labor, IUFD, intrauterine fetal growth restriction, small size for gestational age at birth, stillbirth, and hemorrhage during gestation as well in the postpartum period [4–7].

Recently, data contributed from 15 US states and territories to the National Center for Health Statistics—comparing 44 000 SARS-CoV–infected pregnancies with 1.4 million noninfected pregnancies (April 2020 to August 2021)—demonstrated that preterm labor (at 34–36 weeks' gestation), low birth weight, very low birth weight, and requirement for admission to the neonatal intensive care unit were all higher in SARS-CoV-2–infected pregnancies than in uninfected pregnancies [6]. The Centers for Disease Control and Prevention also reported on birth outcomes among 40 201 pregnant women with COVID-19 infection reported from 31 state and territory health departments through the Surveillance to Emerging Threats to Mothers and Babies Network (SET-NET) [7]. Through 3 December 2021, there were 39 820 live-born infants (99%) and 381 pregnancy losses (1%) reported in this data set. Of the 37 553 pregnancies with data available on delivery, 18% represented infections in the first trimester (first 14 weeks), 31% in the second trimester (14–27 weeks), and 51% in the third trimester (27–40 weeks). Preterm birth (before 37 weeks' gestation) occurred in 3704 (10%) of affected pregnancies. Premature rupture of membranes, induction of labor, cesarean section, preterm birth, fetal growth restriction, and

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postpartum hemorrhage were all more accentuated in the setting of first-trimester infection. Of the 5460 infants (15%) who had SARS-CoV-2 laboratory testing, only 8% had detectable virus at delivery.

Placental abnormalities have been increasingly documented in the setting of symptomatic or asymptomatic SARS-CoV-2 infection in pregnant women. The majority of evaluated placentas have not had demonstrable virus present, despite presence of an array of nonspecific pathologic placental abnormalities. A review of 20 studies focused on pathologic evaluation of the placental effects of maternal SARS-CoV-2 infection in third-trimester placentas demonstrated fetal vascular malperfusion in a third of cases and maternal vascular malperfusion in nearly half of them, along with evidence of placental inflammation in a smaller percentage of cases (villitis in 8.7%, intervillositis in 5.3%, and chorioamnionitis in 6%), although most studies lacked a control group [8]. Of those tested, a minority of neonates (2%) and placental samples (21%) tested positive for SARS-CoV-2 infection. Another comprehensive review of placental abnormalities in the setting of SARS-CoV-2–infected pregnant women included diffuse perivillous fibrin, fetal vascular malperfusion evidenced by thrombi in the fetal vessels, choriohemangioma, maternal vascular malperfusion, and multifocal infarctions [9].

In the current review, virus was also detected in the minority of placentas, suggesting that the placenta is susceptible to the effects of maternal COVID-19 disease distinct from direct viral effects. It was also noted that maternal comorbid conditions, such as hypertension, preeclampsia, and gestational diabetes, could also contribute to these pathologic findings. Although inflammation may be partially responsible for placental pathology, another 2020 study documented findings such as perivillous fibrin, fetal and/or maternal vascular malperfusion with intervillous thrombi and vessel abnormalities, and multifocal infarction, in the absence of acute or chronic inflammation, suggesting direct vascular effects, including arteriolar atherosis, and fibrinoid necrosis [9]. Other studies have suggested that maternal and/or fetal malperfusion, may have a relationship to altered coagulative or microangiopathic state induced by SARS-CoV-2 [10]. Another comprehensive review of the complex pathophysiology of placental injury in the setting of SARS-CoV-2 infection included comments on the contribution of angiotensin-converting enzyme 2 receptor expression within the placenta as well as other factors, such as protease expression, and activation of the interferon (IFN) pathway [11]. Despite these studies, the precise mechanisms of placental injury are still not clear and require further evaluation, ideally with appropriate controls to better discern nonspecific versus SARS-CoV-2–specific effects and mechanisms of injury.

In the current issue of *The Journal*, Guan et al [1] present a detailed analysis of a single IUFD resulting from infection with Delta-variant SARS-CoV-2 during the third trimester of pregnancy and placental abruption. Histopathologic evaluation of the placenta did not reveal malperfusion, viral inclusions, erythroblastosis, villous edema, suspicious lesions on the placental disk, membrane inflammation, or umbilical cord phlebitis or arteritis. However, there was abundant intervillous inflammation, composed of neutrophils and monocytes diffusely involving the placenta. SARS-CoV-2 antigen was present diffusely through the placental disk in villous cytotrophoblasts and throughout the cytoplasm of syncytiotrophoblasts. Compared with expression in a control placenta from a healthy woman, levels of 9 of 13 proinflammatory markers associated with viral infection were dramatically increased in the COVID-19–infected placenta, including tumor necrosis factor α (increased nearly 200-fold), IFN-γ–induced protein 10 (80-fold), IFN-α (>50-fold), interleukin 6 (19-fold), IFN-γ (17-fold), interleukin 8 (13-fold), monocyte chemoattractant protein 1 (CCL2) (12-fold), interleukin 10 (10-fold), and granulocyte colony-stimulating factor (4-fold). Guan et al present a highly plausible mechanism of IUFD, namely, that the virus-induced proinflammatory state was associated with trophoblastic necrosis and lesions crossing the placenta, ultimately leading to placental abruption [1].

Also in this issue of *The Journal*, Shook et al [2] present a case series of Delta-variant SARS-Co-V-2–associated maternal infection, with resultant IUFD in 2 cases, 1 with resultant severe neonatal illness. In all 3 cases, placentitis was noted to be the likely mechanism of disease, particularly since the live-born infant was PCR negative for SARS-COV-2 despite severe symptoms. These authors have previously reported on the rarity of maternal viremia and placental infection with SARS-CoV-2 and the absence of specific placental histopathologic signature associated with COVID-19 in pregnancy. In contrast, they now highlight that Delta-variant SARS-CoV-2 infection may result in maternal viremia, placental SARS-CoV-2 infection, and severe placentitis, associated with fetal compromise. Gross and histopathologic placental sections for each case are presented, including characteristic patterns of placentitis and demonstration of SARS-CoV-2 RNA by in situ hybridization staining to corroborate SARS-Cov-2 placental infection. Shook et al place these findings in the context of recently published data from the Centers for Disease Control and Prevention, demonstrating a 4-fold risk of stillbirth in SARS-CoV-2–positive compared with SARS-CoV-2–negative pregnant individuals during the epoch of the Delta variant.

Taken together, it is increasingly evident that SARS-CoV-2 infection is associated with both increased risk of severe disease in pregnant mothers and increased risk of adverse pregnancy outcomes, which may vary with specific circulating variants. These studies are important additions to the growing body of evidence that SARS-CoV-2 infection in pregnancy can be detrimental not only to the pregnant woman but also to the fetus via pathologic effects on the placenta. Placental injury may result from inflammatory or vascular effects

in the presence or absence of inflammation, which ultimately are detrimental to the fetus, even without demonstrated direct viral infection of the fetus.

Despite these possible effects, the uptake of SARS-CoV-2 vaccination in pregnant women has been suboptimal. As of 1 January 2022, the majority of pregnant women in the US have not been vaccinated; 41.5% of pregnant women have been vaccinated, with 24.7% receiving their vaccine during pregnancy [12]. Although pregnant women were not included for enrollment into the initial SARS-CoV-2 vaccine clinical trials leading to emergency use authorization, use in pregnant women has been tracked carefully, including in programs such as the Vaccine Adverse Event Reporting System (VAERS), V-safe, and the Vaccine Safety Data Link. Reports published in 2021 demonstrated both efficacy and safety in pregnancy, with no increase or pregnancy loss in vaccinated as compared to nonvaccinated women [13, 14]. Additional data have emerged documenting transfer of potentially protective passively transmitted antibody from mother to infant, which is of additional potential benefit to these young infants. This is particularly relevant and another important potential benefit of maternal vaccination, since infants are not yet eligible for vaccination yet have one of the highest rates of hospitalization for SARS-CoV-2 infection among children [15]. COVID-19 vaccination is recommended for women who are pregnant or breastfeeding, are currently trying to get pregnant, or might become pregnant in the future. The studies presented in this issue should provide further impetus for pregnant women and their care providers to seek vaccination to minimize SARS-CoV-2–induced detrimental health effects to the pregnant mother, the placenta, the fetus and the newborn.

## Notes

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