Abstract: 68S

COVID-19 in Pregnancy: Is the Placenta a Safe Place?

Rebecca Simmons, MD, Thea Golden, PhD, Rebecca Linn, MD, Sneha Mani, PhD,

Perelman School of Medicine, University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia. Pennsylvania, USA

Several large studies have demonstrated that COVID-19 pregnant individuals are at significant risk for severe disease and adverse pregnancy outcomes. The mechanisms underlying these phenomena remain to be elucidated. Although fetal and placental infection is rare, placental abnormalities and adverse pregnancy outcomes associated with placental dysfunction in COVID-19 cases have been widely reported. In particular, placental thrombosis and lesions consistent with maternal vascular malperfusion (MVM) of the placenta are common in individuals with COVID-19. In response to the COVID-19 pandemic, we initiated universal screening (nasopharyngeal swabs) for SARS-CoV-2 at admission to the Penn Health Care System labor and delivery units. Since March 2020, we have analyzed clinical data and placentas from 259 COVID-19 cases and 200 controls. Thirty percent of the COVID-19 cases were diagnosed during the first or second trimester and 70% in the third trimester. Similar to other studies, we observed a significant increase in the incidence of hypertensive disorders of pregnancy (gestational hypertension and preeclampsia, hereafter referred to as GHTN) in COVID-19 cases ($p<0.05$ vs. controls). We also observed a significant increase in preterm birth (PTB) ($p=0.01$ vs. controls). The incidence of SGA (birthweight <10th percentile for gestational age) was increased in COVID-19 cases compared to controls, $p<0.05$) and GHTN was correlated with timing of COVID-19 infection. The incidence of SGA was increased if mothers contracted COVID-19 in the first or second trimester compared to third trimester, while GHTN was increased in patients with COVID-19 in the third trimester ($p<0.05$). Finally, 36% of COVID-19 cases were obese (pre-pregnancy BMI >30) vs. 19% of controls ($p=0.007$) and had more severe COVID-19 disease. Our histology studies showed marked placental pathology in over half of COVID-19 pregnancies. A majority of the COVID-19 placentas had at least one pathologic feature of MVM (62% vs 21%, $p=0.011$). Of those with maternal vascular thrombi, a majority occurred in cases without GHTN, suggesting that the vascular injury may occur through an alternative pathway and be related to the prothrombotic effects of COVID-19. Severe pathologic features of MVM were more likely to occur in patients requiring hospitalization (90%, $p<0.0001$), suggesting severity and temporal relationship of SARS-CoV-2 infection. A subset of COVID-19 placentas showed significant pathology associated with villous syncytiotrophoblast injury (24% vs. 3.7% controls, $p<0.0001$), including increased perivillous fibrin deposition, chronic histiocytic intervillositis, and overt syncytiotrophoblast necrosis/degeneration.

Analysis of the placenta transcriptome revealed a time-dependent effect of SARS-CoV2 infection. When infected early in pregnancy, blood clotting and developmental pathways were altered in the placenta at the time of delivery. When infected later in pregnancy, pathways regulating oxidative stress, mitochondrial dysfunction, and hormone production were altered in the placenta at the time of delivery. Inflammatory pathways were altered independently of the time of infection. These persistent changes in the placenta demonstrate a lasting effect of maternal SARS-CoV2 infection on placental health.

Because SARS-CoV2 does not infect the placenta and placental lesions occur in asymptomatic and mildly symptomatic pregnant women, this suggests an indirect mechanism that is also unrelated to a cytokine storm. Extracellular vesicles released from immune cells may be one such mechanism. While the number of EVs does not change, EVs are smaller in plasma samples of women infected in their first or second trimester compared to healthy controls. This is indicative of a persistent alteration in the biogenesis of circulating EVs. Flow cytometric detection of cell-specific markers identifies the majority of EVs in circulation are from platelets, immune cells, and trophoblasts and the relative proportion is unaltered by infection. Using an in-vitro system, we observed that trophoblast (BeWo) cell incubation with circulating EVs from COVID-19 induced cell death, oxidative stress, and inflammation. Analysis of the transcriptome revealed altered similar pathways seen in the placenta transcriptome. This suggests EVs may be the mediator of the placental dysfunction seen in patients who have an active or resolved SARS-CoV2 infection.