Effects of in Utero SARS-CoV-2 Exposure on Newborn Health Outcomes

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 600 million people worldwide, including millions of pregnant women. While newborns exposed to other viruses in utero are sometimes at high risk for vertical transmission, a substantial body of literature since early 2020 has demonstrated that vertical transmission of SARS-CoV-2 from infected mother to neonate is rare, and that newborns who do become infected with SARS-CoV-2 generally have favorable outcomes. In this review, the authors evaluate the existing literature on vertical transmission of SARS-CoV-2 and its potential mechanisms and discuss short- and long-term health outcomes in newborns who were exposed to SARS-CoV-2 in utero. The authors conclude that vertical transmission and adverse neonatal and infant/child outcomes are unlikely, but that neonates exposed to prenatal maternal SARS-CoV-2 infection may be at slightly higher risk for preterm birth, possibly related to increased risk of severe COVID-19 disease in pregnant women, placental changes, or infection timing. Ultimately, the need for additional and longer-term follow-up data in this population is highlighted.

Two and a half years into the COVID-19 pandemic, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread worldwide. As of this writing (12 September 2022), there have been over 600 million cases globally, with over four million new cases reported in the most recent World Health Organization report for the week of 29 August 2022 ^[1]. The global health burden of COVID-19 disease has affected the entire world, but certain populations, including pregnant women and newborns, have been considered particularly vulnerable to potential adverse outcomes following SARS-CoV-2 infection. One fear among researchers and clinicians early on was the possibility of vertical transmission of SARS-CoV-2 from infected pregnant women to their neonates, but a large body of literature has demonstrated that this occurs in a small proportion of neonates, generally less than 5% ^{[2][3][4][5][6][7]}. Further, rates of neonatal infection do not appear to be increased when newborns breastfeed, room-in, or partake in skin-to-skin care with their mothers ^{[5][6][7]}. Potential mechanisms underlying rare cases of vertical transmission remain unclear, but a prevailing theory is transplacental transmission. Additionally, SARS-CoV-2 has been linked to placental alterations with the capacity to impact newborn outcomes even in the absence of placental infection ^{[8][9][10]}. Available data suggest that newborns exposed to maternal SARS-CoV-2 infection in utero are generally healthy, but that they may be at increased risk of premature birth [6][11][12][13][14]. The literature on longterm outcomes in these newborns is-by definition-limited. Here, the authors review the present data on vertical transmission of SARS-CoV-2 and its potential mechanisms, consider the role of the placenta in neonatal outcomes,

and survey data on short- and long-term outcomes in neonates exposed to maternal SARS-CoV-2 infection in utero (<u>Table S1</u>).

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