What are the perinatal risks of SARS-CoV-2 infection in pregnancy?

Among pregnant women in a large managed care organization, SARS-CoV-2 increased the risk of **prematurity** and **severe maternal morbidity**, but no risk was noted for stillbirth, small-for-gestational age, hypertensive disorders of pregnancy, or adverse neonatal outcomes.

Ferrara A, Hedderson MM, Zhu Y, et al. Perinatal complications in individuals in California with or without SARS-CoV-2 infection during pregnancy. JAMA Intern Med. 2022;182:503-512. doi:10.1001/jamainternmed.2022.0330

EXPERT COMMENTARY BY
Malavika Prabhu, MD, is Assistant Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Weill Cornell Medicine, New York, New York.

FAST TRACK

Study authors aimed to understand if SARS-CoV-2 preceded pregnancies with outcomes such as preterm birth, gestational hypertension, preeclampsia, VTE, gestational diabetes, severe maternal morbidity, hospitalization, and stillbirth

SARS-CoV-2 infection is associated with several adverse outcomes, with the magnitude of specific risks varying by population studied and study design used. Early Centers for Disease Control and Prevention (CDC) data demonstrated that pregnant women were at increased risk for severe illness, including risks of intensive care unit (ICU) admission, invasive ventilation, and extracorporeal membrane oxygenation, compared with non–pregnant women.[1] Since then, other groups have confirmed the increased risks of severe COVID-19, and also identified pregnancy-specific risks, such as preeclampsia, cesarean delivery (CD), prematurity, venous thromboembolic (VTE) disease, and stillbirth.[2-6]

The recent study by Ferrara and colleagues adds more granular data to help refine understanding of COVID-19 in pregnancy and counsel patients.

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Details of the study

The authors conducted a retrospective cohort study between March 1, 2020, and March 16, 2021, using the electronic health records (EHRs) from Kaiser Permanente Northern California, an integrated managed care organization that serves 4.5 million patients annually. Universal testing for SARS-CoV-2 upon admission for delivery began December 1, 2020; prior to this date, asymptomatic pregnant women were tested only for certain criteria (such as being a health care worker or having high-risk medical conditions).

Pregnant women were identified with SARS-CoV-2 based on 1) a positive polymerase chain reaction test result between 30 days prior to the last menstrual period up to 7 days after delivery or 2) an ICD-10 diagnosis of SARS-CoV-2 infection. Pregnant women not meeting these criteria were classified as SARS-CoV-2 negative. Women were followed through pregnancy to understand if they experienced preterm birth (spontaneous and medically indicated), gestational hypertension, preeclampsia/eclampsia, VTE disease, gestational diabetes, severe maternal morbidity (as defined by the CDC), hospitalization, and livebirth (or stillbirth), in order to consider the timing of SARS-CoV-2 infection relative to each of these outcomes (and ascertain whether SARS-CoV-2 infection preceded

any of these outcomes more commonly than not). Management of pregnancies with COVID-19 across this large organization and multiple hospitals was not specified.

Identified perinatal risks

Among 43,886 pregnant women included in the cohort, 1,332 (3.0%) were diagnosed with SARS-CoV-2, with the vast majority of positive tests in the third trimester. Significant sociodemographic differences were noted between those with and without SARS-CoV-2, including differences in age, self-reported race/ethnicity, neighborhood deprivation index, and pre-pregnancy body mass index; no differences were noted for other pre-existing comorbidities, gestational week at delivery, or smoking in pregnancy.

In multivariable models, SARS-CoV-2 infection in pregnancy was associated with severe maternal morbidity, preterm birth, and VTE disease. It was not associated with stillbirth, any hypertensive disorder of pregnancy, CD, or any neonatal complication.

The prevalence of SARS-CoV-2 was 1.3% prior to and 8.0% after implementation of universal testing in pregnancy for SARS-CoV-2. No differences were noted in the risks of severe maternal morbidity or preterm birth relative to the implementation of universal testing, with risks remaining comparably high even after universal testing.

A total of 307 of the 1,332 pregant women with SARS-CoV-2 were admitted to the hospital for symptomatic infection; 3 required noninvasive positive-pressure ventilation, and 1 required mechanical ventilation.

Study strengths and weaknesses

Strengths include the large, EHR-based dataset from a single organization, allowing for granular analysis on patient comorbidities and outcomes (rather than only based on diagnosis codes, as is true of many other large databases), as well as focus on relevant perinatal outcomes and thoughtful statistical modeling. However, a significant challenge with this, and many other studies, is ascertainment of SARS-CoV-2 infections throughout pregnancy. Asymptomatic and mildly symptomatic women, who may not be as likely to have adverse pregnancy outcomes, can often be counted in the unaffected population, biasing study results toward increased risks of SARS-CoV-2. Although the findings stratified by implementation of universal testing (which captures a greater fraction of asymptomatic patients at admission for delivery), do not suggest risk mitigation with asymptomatic status, this analysis did not capture asymptomatic infections earlier in pregnancy, many of which might not be associated with perinatal risk.

Another challenge with such a dataset is that one cannot determine the severity of illness of each patient without manual review of each chart; however, other data that are easily abstracted from the EHR may serve as a proxy. For instance, of the 307 women with symptomatic COVID-19, 4 required respiratory support above nasal cannula. This suggests a low rate of severely ill women, and may explain some of the findings in the study, such as no differences in the rate of CD, hypertensive disorders of pregnancy, or stillbirth, but does not explain the increased risk of both medically indicated and spontaneous preterm birth, or the rates of acute respiratory distress syndrome and sepsis that drive the increased risk of severe maternal morbidity.

The CDC has published data on the risks of stillbirth from a large hospital-based administrative database for COVID-19 from Premier Healthcare.[2] In a cohort of over 1.2 million women admitted for delivery, including the timeframe of Ferrara et al's study, COVID-19 was associated with a 2-fold increased risk of stillbirth, with higher risks noted with the delta variant. A rare outcome, stillbirth occurs in 6/1,000 births,[7] which was the rate seen in

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

These data continue to support that SARS-CoV-2 infection is associated with prematurity, VTE, and severe maternal adverse outcomes. As sports fanatics often state, the best defense is a good offense. In the case of SARS-CoV-2, COVID-19 vaccination, mask wearing, and physical distancing are likely the best offense against COVID-19 infection in pregnancy.

FAST TRACK

A challenge with COVID-19 studies is that infection may not be identified in asymptomatic women, who may not be as likely to have adverse outcomes, biasing results toward increased risks of SARS-CoV-2 in pregnancy

Ferrara's publication for both women with and without SARS-CoV-2 infection. The rare nature of the outcome may explain why a signal was not noted in the article of interest.

Translating data to patient counseling

Ferrara and colleagues' study clearly confirms that COVID-19 infection has risks. Although many women with a COVID-19 infection in pregnancy may have an uncomplicated course, a favorable outcome is hard to predict with certainty. Risks of prematurity, VTE, organ dysfunction, and stillbirth from COVID-19 are rare but devastating complications. However, vaccinated women tend to incur far fewer adverse outcomes of COVID-19 in pregnancy, namely a 90% risk reduction in severe or critical COVID-19, with lower rates of ICU admissions and stillbirths.[8] While these data strongly favor vaccination, we remain ill-advised on management strategies specifically to mitigate risk for the pregnancy once affected by COVID-19 infection. Thus, prevention with vaccination, mask wearing, and physical distancing remains a cornerstone of prenatal care in the current day. ●

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