What placental mechanisms protect the fetus from harm in the setting of maternal COVID-19 infection?

Lower placental ACE2 protein levels observed in cases of third trimester maternal COVID-19 infection may be evidence of a protective response, according to a cohort study of 24 individuals from whom placenta and maternal serum samples were obtained at delivery

Taglauer ES, Wachman EM, Juttukonda L, et al. Acute severe acute respiratory syndrome coronavirus 2 infection in pregnancy is associated with placental angiotensin-converting enzyme 2 shedding. Am J Pathol. 2022;192:595-603. doi.org/10.1016/j.ajpath.2021.12.011

EXPERT COMMENTARY
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Although transmission of SARS-CoV-2 virus from an infected mother to her fetus is rare, placental infection with SARS-CoV-2 can occur and has been observed in association with placental damage and adverse pregnancy outcomes, including stillbirth.[1] Understanding what mechanisms of defense protect the placenta and fetus from direct SARS-CoV-2 infection at the maternal-fetal interface, as well as the factors that might disturb or enhance that protection, is critical to gaining a deeper understanding of the potential impact of maternal COVID-19 on fetal well-being.

Details of the study

In a cohort of 24 pregnant individuals, Taglauer and colleagues investigated levels of placental angiotensin-converting enzyme (ACE)-2, placental ADAM17 (a disintegrin and metalloprotease domain 17) activity, and maternal serum soluble ACE2 in samples obtained at delivery from individuals with a history of second trimester COVID-19 infection, early third trimester COVID-19 infection, and no history of COVID-19 infection.

Results. Maternal COVID-19 infection in the early third trimester of pregnancy resulted in lower ACE2 protein levels in the placenta at delivery, higher *ACE2* gene expression, and an increase in ADAM17 activity, compared with infection in the second trimester of pregnancy and compared with noninfected controls.

The authors postulated that increased ADAM17 activity—the enzyme responsible for ACE2 cleavage and shedding—may be responsible for lower ACE2 protein levels. Soluble ACE2 levels in maternal blood at delivery were increased in individuals with third trimester COVID-19 infection, although the source of soluble ACE2 (placental or otherwise) could not be determined with the methods employed. Levels of placental estrogen were no different between groups, which suggests that estrogen is not responsible for the observed differences.

Study strengths and limitations

ACE2 is the main receptor for the SARS-CoV-2 virus and facilitates viral entry into the cell.[2]

FAST TRACK

Compared with maternal COVID-19 infection in the second trimester and with noninfected controls, early third trimester maternal infection resulted in lower ACE2 protein levels in the placenta at delivery, higher ACE2 gene expression, and an increase in ADAM17 activity

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

As the number of pregnancies exposed to COVID-19 continues to grow worldwide, how immune defenses at the maternal-fetal interface protect against fetal infection remains an important area of investigation.

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Key points: COVID-19 infection and vaccination in pregnancy[a]

- Pregnant people are at increased risk of more severe COVID-19 illness.
- The risk of stillbirth is 2- to 4-fold higher in women with COVID-19 infection during pregnancy.[1]
- COVID-19 vaccination is recommended for all people who are pregnant, lactating, or considering pregnancy.
- Pregnant and recently pregnant people up to 6 weeks postpartum should receive a third "booster" dose of a COVID-19 mRNA vaccine following completion of their initial COVID-19 vaccine or vaccine series.
- The mRNA COVID-19 vaccines are preferred over the Johnson & Johnson/Janssen COVID-19 vaccine for pregnant and lactating individuals for primary series and booster vaccination.
- Completion of a 2-dose mRNA COVID-19 vaccination series during pregnancy might help prevent COVID-19 hospitalization among infants <6 months.[2]

[a]Vaccine recommendations adapted from: ACOG practice advisory: COVID-19 vaccination considerations for obstetric-gynecologic care. Last updated March 2, 2022. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care. Accessed March 21, 2022.

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Placental villous cells that are in direct contact with maternal blood express the ACE2 protein, rendering them potentially vulnerable to SARS-CoV-2 infection.[3] In this study, the authors observed lower placental ACE2 protein in term placentas from recent (early third trimester) but not remote (second trimester) maternal SARS-CoV-2 infection, arguably the result of the observed increase in ADAM17 cleavage activity. Prior studies have shown conflicting results, with equal or higher ACE2 levels noted in the setting of maternal COVID-19 infection, which may be related to differences in COVID-19 disease severity, gestational age of infection, and/or fetal sex in these cohorts.[4-6]

The concept that increased placental ACE2 shedding represents a protective defense mechanism that might last weeks beyond the acute infectious period is intriguing, but it requires further study. Observed differences in third but not second trimester COVID-19 infections could indicate either 1) an effect of maternal COVID-19 infection that lasts for several weeks but eventually normalizes over time, in the case of a remote infection; or 2) that second trimester maternal COVID-19 infection does not have the same pronounced effect on ACE2 levels as does third trimester infection. Observational studies of the human placenta are not able to answer this question, as directly sampling the placenta at the time of the exposure (or repeated sampling over time) in ongoing pregnancies is neither practical nor ethical. Further studies using animal or cellular models of SARS-CoV-2 infection in pregnancy may be necessary to fully understand the clinical relevance of these findings.

The study by Taglauer and colleagues provides a compelling argument for exploring how immune defenses at the maternal-fetal interface evolve over time and vary by trimester of exposure. ●

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