

EDITORIAL

Can SARS-CoV-2 Infection Be Acquired In Utero? More Definitive Evidence Is Needed

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Two articles reported in this issue of *JAMA* from separate research teams in China present details of 3 neonates who may have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in utero from mothers with coronavirus disease 2019 (COVID-19).^{1,2} Evidence for such transmission

is based on elevated IgM antibody values in blood drawn from the neonates following birth. All infants also had elevated IgG antibody values and cytokine levels, although these may have crossed the placenta from the mother to the infant. No infant specimen had a positive reverse transcriptase-polymerase chain reaction test result, so there is not virologic evidence for congenital infection in these cases to support the serologic suggestion of in utero transmission. Nevertheless, the serologic data are provocative for a virus that is believed to be spread by respiratory secretions and—given the modeling showing that a significant percentage of the world's population, many of them pregnant women, will be infected over the next weeks or months—it is one that deserves careful consideration. However, at this time, these data are not conclusive and do not prove in utero transmission.

These 2 research teams deserve credit for exploring the possibility of vertical transmission in neonates delivered to pregnant women with COVID-19, especially during the difficult period of a surge in cases at the onset of what would become a worldwide pandemic. However, the suggestion of in utero transmission rests on IgM detection in these 3 neonates, and IgM is a challenging way to diagnose many congenital infections. IgM antibodies are too large to cross the placenta and so detection in a newborn reasonably could be assumed to reflect fetal production following in utero infection. However, most congenital infections are not diagnosed based on IgM detection because IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges.³

Sensitivity and specificity of IgM tests vary by disease but usually are less reliable than molecular diagnostic tests based on nucleic acid amplification and detection. For example, first-generation IgM enzyme-linked immunosorbent assay testing for congenital cytomegalovirus infection had a sensitivity of approximately 70% and a specificity of nearly 95%,⁴ with solid-phase radioimmunoassay IgM detection increasing the sensitivity to 89%.⁵ Both are markedly lower than the near-100% sensitivity and specificity of urine and saliva polymerase chain reaction detection of cytomegalovirus DNA.⁶ In congenital rubella syndrome, false-positive

IgM results may occur because of the presence of rheumatoid factor or incomplete removal of IgG, which may be maternal in origin.⁷ IgM detection plays no role in the diagnosis of congenital syphilis, although this has been an area of research interest.^{8,9} While antibody panels including IgM along with IgG and IgA are used in the diagnosis of congenital toxoplasmosis, the sensitivity of IgM alone is in the range of 54% to 76%.^{10,11} IgM testing in congenital Zika infections is complicated by false-positive results due to nonspecific reactivity or cross-reactivity with other flaviviruses.¹²

Additionally, the kinetics of decline of SARS-CoV-2 IgM detailed in the study by Dong et al¹ are unusual compared with rates of decline in other congenitally transmitted infections. The neonate's IgM value declined from 45.83 AU/mL at 2 hours of life to 11.75 AU/mL on day 14 of life, just above the threshold of 10 AU/mL that constitutes a positive result. This decline in IgM concentration is very rapid. In infants with congenital rubella syndrome, rubella-specific IgM can be detected for several months, with about a third having detectable IgM from 6 months to 2 years of age.¹³ Likewise, IgM following congenital Zika infections can persist for a year or longer.¹⁴ While the kinetics of IgM production and decay in SARS-CoV-2 infections are not yet known, the rapid decline reported in this patient, along with the inherent challenges with false-positive IgM test results in other congenital infections, raises the possibility that the laboratory findings in these 3 infants are not evidence of true congenital infection but rather could represent artifact.

In the report from Dong and colleagues,¹ the sensitivity and specificity of their IgM assay were 70.2% and 96.2%, respectively, with the citation being a study in the *Chinese Journal of Laboratory Medicine*, from which only the abstract is available in English. Zeng and colleagues² reported a sensitivity of 88.2% and specificity of 99.0% based on data from the manufacturer. Thus, data supporting these performance characteristics of the SARS-CoV-2 IgM assays used in these reports are lacking for our review. With such a rapidly developing clinical situation encompassing the entire world, this is not surprising or a criticism. But it is a caution in interpreting the results reported in these 2 Research Letters. Is it possible that SARS-CoV-2 can be transmitted in utero? Yes, especially because virus nucleic acid has been detected in blood samples.¹⁵ Is it also possible that these results are erroneous? Absolutely. Although these 2 studies deserve careful evaluation, more definitive evidence is needed before the provocative findings they report can be used to counsel pregnant women that their fetuses are at risk from congenital infection with SARS-CoV-2.

ARTICLE INFORMATION

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