EDITORIAL

Can We Protect Pregnant Women and Young Infants From COVID-19 Through Maternal Immunization?

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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy and early infancy can result in severe disease.[1-3] Less is known about the immune responses of pregnant women with coronavirus disease 2019 (COVID-19) and the possibility for infant protection. Vaccination of pregnant women with SARS-CoV-2 vaccines in development has begun in the United States in the context of emergency use authorized vaccine deployment for high-risk priority groups and guidance from the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices and the American College of Obstetrics and Gynecology.[4-8] Therefore, it is imperative to better understand the potential of immunization during pregnancy for maternal and infant disease prevention and for the implementation of pandemic control strategies.

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In this issue, Flannery et al[9] report on a large study including 1714 pregnant women who delivered newborns in the northeastern United States during the early stages of the COVID-19 pandemic, from April to August 2020. Investigators collected discarded maternal and cord blood sera from 1471 eligible mother-newborn pairs to measure IgG and IgM antibodies to the receptor-binding domain of the SARS-CoV-2 spike protein by enzyme-linked immunosorbent assay and assess antibody concentrations and transplacental transfer, contributing useful data to assess the potential for protection of infants in early life.

While only 83 women (6% of the study population) had detectable IgG and/or IgM antibodies at delivery, the majority of infants born to seropositive mothers (72 of 83 [87%]) had detectable IgG antibody at birth. As expected, given the process of active IgG transplacental transfer during pregnancy, transfer ratios were more than 1.0, and there was a positive correlation between maternal and infant antibody titers. However, infants born to mothers with very low IgG levels were seronegative at birth. Interestingly, transplacental transfer was efficient regardless of the presence of symptoms in the mother or the severity of disease. This unique observation was possible because of the use of serologic testing for the diagnosis of infection, which allowed the ascertainment of asymptomatic infection at any time during pregnancy, independently from molecular testing at the time of symptoms or admission for delivery. Notably, most seropositive women (50 of 83 [60%]) were asymptomatic. It is possible that women with moderate or severe COVID-19 could have higher antibody concentrations to transfer; studies with more patients in these symptomatic disease categories could help answer this question.

The time available for antibody transfer is another important factor. Flannery et al[9] were able to ascertain that placental transfer ratios increased when the time between maternal infection and delivery was longer. This finding is consistent with similar observations on the transfer of antibodies in recent studies of a respiratory syncytial virus vaccine given during pregnancy, where an interval of 30 days or more from vaccination to delivery was significantly associated with higher antibody transfer.[10] Interestingly, the transfer ratio of SARS-CoV-2 antibodies was not affected by premature delivery (gestational age at birth, <37 weeks) in this study, where the most preterm infant was born at 31 weeks of gestation. Protection in infants born prematurely may be affected by placental function and a shorter time for antibody transfer; therefore, studies with larger sample size and prospective follow-up are needed to address this observation for COVID-19.

Transplacental transfer of antibodies is selective for IgG; therefore, it is not expected to find IgM antibody in cord blood unless it is produced by the fetus, as seen in true congenital infections such as cytomegalovirus or rubella. In this study, no evidence of intrauterine or postnatal infection was identified through serology, viral detection, or clinical findings. The authors observed that infants whose mothers had only IgM detected, not IgG, were seronegative at birth. Therefore, these infants were potentially unprotected despite documented maternal infection. Maternal infection shortly before, during, or after delivery, when sufficient IgG antibody is not available for transplacental transfer, results in ongoing vulnerability of the infant who could become infected if exposed to the mother (asymptomatic or symptomatic) or other infected household contacts. While there is a potential for some protection from breast milk antibodies in lactating infants, this might be limited and less effective than protection from transplacental antibodies. The susceptibility of these infants deserves special attention, as it is reminiscent of neonatal varicella infection, which results in higher likelihood of infection and more severe neonatal disease in infants born to mothers infected perinatally who are unable to provide passive protection to their newborns. There are still insufficient data on the severity of COVID-19 disease in infants born with or without maternal antibodies.

The study of Flannery et al,[9] along with similar observations in various reports of COVID-19 infection during pregnancy, has important implications for pandemic control through vaccination, specifically, to inform maternal and infant vaccination strategies.[11-15] While transplacental transfer ratios may vary, it is reassuring that maternal infection, whether symptomatic or asymptomatic, results in sufficient antibody

production for an efficient transplacental antibody transfer to newborns of infected mothers because maternal vaccination could do the same. However, the timing of maternal vaccination to protect the infant, as opposed to the mother alone, would necessitate an adequate interval from vaccination to delivery (of at least 4 weeks), while vaccination early in gestation and even late in the third trimester could still be protective for the mother. When considering that up to 2 weeks from complete vaccination (2-dose series with an interval of 21 or 28 days or more between doses with current COVID-19 vaccines) is necessary for higher efficacy of the vaccine and that transplacental transfer begins around 17 weeks of gestation increasing exponentially as gestation advances and the placenta grows, maternal vaccination starting in the early second trimester of gestation might be optimal to achieve the highest levels of antibodies in the newborn. While a serologic correlate of protection against SARS-CoV-2 infection and symptomatic or severe disease is unknown at this time, higher antibody levels might result in a better chance for protection of the newborn during a period of special vulnerability.

In addition to identifying serologic correlates of protection, several important factors remain to be elucidated to consider maternal immunization for the protection of infants, including the kinetics and duration of maternally derived antibodies in infants and their neutralizing activity and efficacy against COVID-19. If what we know about other important vaccine-preventable diseases in infants for which maternal vaccination is recommended (tetanus, pertussis, influenza) or under investigation (respiratory syncytial virus) holds true, transplacentally acquired antibody rapidly decays by the second month of life and continues to drop so that by 6 to 12 months, the protective efficacy is reduced. Available data on the effect of COVID-19 in newborns and infants suggests that severe disease may occur in early life.[3,14] Could maternal antibodies help delay the onset of infection or protect the infant from becoming infected, having severe disease, or dying of COVID-19? To what extent can antibodies transferred through breast milk protect lactating newborns? Should infants be vaccinated regardless of maternal infection, and if so, what is the best timing to initiate infant vaccines? Is there a potential detrimental effect of maternal antibodies on infant responses to active immunization? And what would be the optimal vaccine and vaccination regimen for infants, considering their risk and unique immunologic needs? While maternal immunization is likely the best available option to protect both pregnant and lactating mothers as well as their infants during the COVID-19 pandemic, the importance of collecting data to answer these outstanding questions cannot be overemphasized. Critical information needs to be collected through carefully designed prospective or longitudinal clinical studies to inform and implement safe and effective maternal and infant vaccination strategies.

ARTICLE INFORMATION

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