

# Does Maternal COVID-19 Infection Offer Protection to her Newborn? Will Maternal Immunization for COVID-19 Do the Same? Unresolved Questions, Awaiting Answers

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In the October 2020 Neonatology Today commentary, data were high-lighted from the American Academy of Pediatrics Perinatal COVID-19 Registry of more than 3000 deliveries that found about 2% of infants born to women with SARS-CoV-2 positive tests also tested positive within four days of birth, reflecting very infrequent vertical transmission (1). Thus the vast majority of newborns who are symptomatic shortly after birth are unlikely to have had a vertical transmission of the virus (2,3). Maternal-Fetal Medicine physicians and Neonatologists are now in an era when the vaccination of pregnant women and others with SARS-CoV 2 vaccines occurs under emergency use authorized vaccine deployment for the high-risk groups. With guidance from the US Centers for Disease Control, the Prevention Advisory Committee on Immunization Practices, and the American College of Obstetricians and Gynecology, pregnant women are encouraged to receive vaccination using one of the authorized vaccines (4-8). Detection of maternal infection and neonatal infection or immunity from transplacental acquired maternal antibody after maternal COVID-19 infection is essential for evaluating infant protection or attribution to SARS-CoV-2 infection.

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Flannery et al. report that among 1714 pregnant women who delivered newborns in the early stages of the COVID-19 pandemic (April to August 2020 (9) using maternal and cord blood sera from 1471 eligible mother-infant dyads. They measured IgG and IgM antibodies to the receptor-binding domain of the SARS-CoV-2 spike protein using enzyme-linked immunosorbent assays to assess maternal antibody concentrations and transplacental transfer to infant cord blood. These data were analyzed to assess the potential for determining "levels of protection" for infants during the newborn period. Eighty-three women (8%) of the study population had detectable IgG and/or IgM antibodies at delivery, with 87% of infants born to seropositive mothers having detectable IgG at birth. IgG transplacental transfer rates were >1.0. There was a positive correlation between maternal and infant antibody titers. However, infants born to mothers with very low IgG levels had undetectable IgG levels at birth. They noted that transplacental transfer was efficient regardless of maternal severity symptoms or illness from COVID-19. Most seropositive women (60%) were asymptomatic. Mothers with moderate or severe COVID-19 infec-

tions may have had a higher RBD receptor-binding domain. This domain is the part of the antibody to the spike protein that directly binds to the receptor in concentrations potentially high enough to transfer protection to the newborn. This latter group of mothers and infants should further be evaluated as no definitive answer can be gleaned from this report.

The timing of the transfer of antibodies was also evaluated by Flannery et al., who determined that placental transfer ratios increased when the time between maternal infection and delivery was longer. This finding is similar to the report by Madhi and co-workers (10) on Respiratory Syncytial Virus vaccination during the last trimester of pregnancy (maternal RSV F protein nanoparticle vaccination) who found higher antibody transfer when >30 days elapsed between maternal immunization and significantly lower respiratory tract infections or infants with severe hypoxemia in the first 90 days after birth.

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Flannery and coworkers report that the transfer ratio of SARS-CoV-2 antibodies was not affected by premature delivery; however, in their study, a few extremely low birth weight or very low gestational age were included (lowest gestational age 31 weeks). Protection of prematurely born infants may be affected by placental function and a shorter time for placental-fetal transfer of antibody. The transplacental transfer was selective for IgG, and IgM antibodies in the cord blood were not found. Neonatologists are more familiar with both antibodies' patterns to be found when an intrauterine viral infection has occurred or when the virus is isolated from sera or cerebrospinal fluid of newborns. These investigators found that infants whose mothers had only IgM detected, but not IgG, were seronegative at birth, and these infants may have been unprotected despite documentation of maternal infection. Atyeo and colleagues (10) report using systems serology to characterize the Fc profile of influenza, pertussis, and SARS-CoV-2 specific antibodies transferred across the placenta. While influenza and pertussis specific antibodies were actively transferred, SARS-CoV-2 specific antibody transfer was significantly reduced compared to influenza and pertussis antibodies, and cord blood titers and functional activity were lower than in maternal plasma. This effect was noted only when COVID infection during the third trimester. Edlow et al. studied 127 pregnant women, 64 of whom were RT-PCR positive for SARS-CoV-2, and 63 were negative. Women with COVID-19 infections ranged from 36% being asymp-

tomatic, 34% with mild, 11% with moderate, 16% with severe disease, and 3% with critical disease. In viral load analyses among 107 women, there was no detectable viremia in maternal or cord blood and no evidence of vertical transmission. Maternal to the neonatal transfer of SARS-CoV-2 antibodies were significantly lower than the transfer of hemagglutinin A antibodies to influenza. They concluded that transplacental transfer of SARS-CoV-2 antibodies is "inefficient." (11). Although these studies confirm very low vertical transmission, the infants' degree of protection seems to be consistent. The question of how well antibodies capable to "neutralize" the coronavirus rather than total IgG requires further study.

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Maternal infection shortly before or after delivery where sufficient IgG antibody is not available for transplacental transfer leaves newborns unprotected if exposed to their mother whether she is symptomatic or asymptomatic and to others. Pace and coworkers analyzed breast milk and breast cultures from 37 COVID-19 positive mothers (12) and found SARS-CoV-2 RNA from breast skin swabs but none in breast milk samples. All milk contained SARS-CoV-2 specific IgA and IgG, and levels of IgA correlated with SARS-CoV-2 neutralization. Centeno-Tablante et al. (13) performed a systematic review of transmission of SARS-CoV-2 through breastfeeding and breast milk. They report that 9 of 68 breast milk samples analyzed from women with COVID were positive for SARS-CoV-2 RNA, and of the exposed infants, four were positive, and two were negative for COVID 19. They concluded there is "no evidence" of SARS-CoV-2 transmission through breast milk."

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While transplacental transfer ratios may vary, it is reassuring that maternal infection (symptomatic or asymptomatic) results in sufficient antibody production for an efficient transfer to the newborns delivered of mothers with prior infection earlier in pregnancy. Whether or not maternal vaccination to COVID-19 will provide similar protection is unknown. These unanswered questions regarding the timing of maternal immunization, vaccine type, number of doses, the elapsed time between immunization and birth may be critical for neonatal protection since the transplacental transfer of antibodies begins with about 10% of maternal antibody transferred by 17-27 weeks gestation that increases as gestation

progresses (14,15). Whether maternal vaccination starting in the early second trimester of pregnancy might be optimal to achieve the highest levels of maternal IgG antibodies passively transferred to the fetus and thereby the cord blood is unknown. Whether the kinetics and duration of maternally derived antibodies and their neutralizing capacity correlate with other recommended vaccinations (e.g., pertussis and influenza) during pregnancy are similar among women immunized against COVID-19 protects their infants against SARS-CoV-2, and whether the duration of effective antibody concentrations in newborns over the first months of after birth will be protective is unknown. This question will require further studies with each of emergency use authorized vaccines. Different vaccines administered at different times during pregnancy and in different dosing strategies undoubtedly influence their immunogenicity and potential for maternal transplacental IgG transfer to the fetus and newborns. Mutant viruses may or may not be neutralized by current vaccines. As of January 24, 2021, 8,633 women were vaccinated with the Pfizer=BioNTech and 6498 with the Moderna vaccine (16). Dr. Anthony Fauci noted on February 1, 2021, that about 10,000 pregnant women in the U.S. had been vaccinated since the Food and Drug Administration authorized two vaccines, and so far, there have been "no red flags" (17). The CDC Vaccine Safety Team has created a registry of pregnant women receiving the vaccine. Both CDC and the Advisory Committee on Immunization Practices (ACIP) have endorsed immunization against during pregnancy in the U.S. Vaccinations during pregnancy has yet to be recommended during pregnancy in some European countries as of December 2020. (18) Furthermore, the United Kingdom National Health Service advises against vaccination during pregnancy until there are "high risk" conditions on January 29, 2021, and immunization while breastfeeding requires consultation with a physician (19). Finland has taken the position that the decision to immunize should be made on an individual basis after a discussion between the pregnant woman and her obstetrician (20).

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Pregnant women were not part of the safety and efficacy trials. Those who were immunized may have received the vaccine before their confirmation of pregnancy. Focused trials on sufficient numbers of pregnant women will be necessary to address these questions. Such trials will be a challenge, but not an insurmountable one. Neonatologists should focus on the measurement of SARS-CoV-2 IgG and neutralizing antibody or RBD IgG levels in cord blood as an indicator for intrauterine infection. Regardless of maternal status, except when mothers are critically ill, encouraging breastfeeding affords additional protection for the infant.

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