VIEWPOINT

COVID-19 Vaccination in Pregnant and Lactating Women

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Pregnant women with severe or critical coronavirus disease 2019 (COVID-19) infection are at increased risk for preterm birth and pregnancy loss. In studies of hospitalized pregnant women with COVID-19, which have included between 240 and 427 infected women, the risk for preterm delivery (both iatrogenic and spontaneous) has ranged from 10% to 25%, with rates as high as 60% among women with critical illness.[1] The primary risk to a pregnancy appears to be from maternal illness. In addition, pregnant women may be at higher risk for severe illness and death caused by COVID-19 compared with nonpregnant women. In an analysis of national surveillance data that included pregnancy status of 409 462 women with symptomatic COVID-19 illness through October 3, 2020, the adjusted risk ratio in pregnant women (vs those of similar age and not pregnant) was 3.0 for intensive care unit admission, 2.9 for mechanical ventilation, and 1.7 for death.[2] Thus, preventing critical COVID-19 infection is important for both mother and fetus.

It is now clear that early neonatal COVID-19 infections are rare, but whether maternal immune response to infection protects the fetus remains unknown. Despite reports of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG detected in newborns with negative IgM and negative results on polymerase chain reaction, SARS-CoV-2–specific antibodies appear to be inefficiently transferred across the placenta following third-trimester maternal infection compared with antibody transfer following infection with influenza or pertussis.[3] Nevertheless, changes in SARS-CoV-2–specific antibody glycosylation patterns and placental selectivity for these antibodies may compensate for suboptimal protection and could be an important lesson for vaccine development. Furthermore, the gestational age of de novo maternal antibody production influences the level of SARS-CoV-2–specific antibody that is detected in cord blood specimens, implying there may be an ideal time for maternal vaccination prior to delivery to optimize protection of the fetus.

Vaccination during pregnancy is common to prevent maternal and infant morbidity from other infectious diseases. Vaccination is specifically recommended to prevent both influenza and pertussis. The clinical data on safety and efficacy of influenza vaccination are abundant. In a randomized trial of 3693 pregnant women in Nepal, influenza immunization was associated with a relative reduction in maternal febrile influenzalike illness by 19% and relative reductions of low birth weight by 15% and infant influenza disease by 30%.[4] These benefits were demonstrated following maternal immunization in either early or late gestation.

Likewise, following early studies that demonstrated rapid decay of maternal pertussis antibody passively transferred to the neonate, a study that included 74 504 mother-infant pairs demonstrated an 85% relative reduction in infant pertussis illness following maternal vaccination in the third trimester compared with postpartum.[5] The Tdap vaccine has been recommended for pregnant women during each pregnancy by the Centers for Disease Control and Prevention since 2012 in an effort to reduce the sharp increase in pertussis cases and deaths that occurred from 2011 to 2012.

While the mRNA platforms of the available COVID-19 vaccines are distinct from both influenza and Tdap vaccines now used during pregnancy, mRNA platforms have been in development for the last decade. Similar mRNA vaccines have been used in clinical trials targeting other infections such as Zika, as well as several types of cancer (such as breast cancer and melanoma).[6] As an immunogenic but noninfectious, nonintegrating platform, mRNA vaccines have potential benefits over live-attenuated virus vaccines, inactivated or subunit vaccines, and DNA-based vaccines. There is no risk of acquiring infection from the vaccine. While no specific studies have evaluated the ability of the lipid nanoparticle vaccine to reach the fetus following vaccination, it is likely that the local muscle cells take up the lipid nanoparticles and initiate transcription to stimulate the immune response.

Even though pregnant and lactating women were not included in the development and clinical evaluation of COVID-19 vaccines and treatments,[7] the US Food and Drug Administration (FDA) and the Advisory Committee on Immunization Practices left open the option for pregnant and lactating women to receive the vaccine. Without data, guidance from professional societies is necessarily vague due to lack of evidence of vaccine efficacy and safety during pregnancy. These organizations must balance the risk of COVID-19 infection to the pregnant and lactating woman with the potential or theoretical risks from the vaccine to the pregnant woman and her developing fetus or the lactating woman and her newborn.

Thus, the guidance from professional societies and agencies has been limited, without an explicit recommendation for COVID-19 vaccination in pregnancy. These societies, including the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, have continued to advocate for making COVID-19 vaccines available to pregnant and lactating women even after the recent statement by the World Health Organization (WHO) on January 26, 2021, explicitly recommending against vaccination of pregnant women using the Moderna vaccine except in select circumstances. The WHO statement[8] was revised on January 29, 2021, to include more permissive language, that "pregnant women at high risk of exposure to SARS-CoV-2 (e.g. health workers) or who have comorbidities which add to their risk of severe disease, may be vaccinated in consultation with their health care provider."

The lack of data for use of mRNA vaccines during lactation is reflected in recommendations from the Academy of Breastfeeding Medicine,[9] which state: "During lactation, it is unlikely that the vaccine lipid would enter the blood stream and reach breast tissue. If it does, it is even less likely that either the intact nanoparticle or mRNA transfer into milk. In the unlikely event that mRNA is present in milk, it would be expected to be digested by the child and would be unlikely to have any biological effects."

The organization further states that potential unknown risks should be weighed against the potential benefit of neonatal protection from infection via passive transfer of antibodies from breast milk.

Given the continued advocacy by obstetric societies for inclusion of pregnant and lactating women in the initial large clinical efficacy trials, why is there such limited evidence to guide vaccination recommendations? A major reason neither pregnant nor lactating women were included in COVID-19 vaccine trials is the concern of liability over the potential adverse effects on a fetus of a new product administered in pregnancy. This lack of inclusion of these populations in new therapeutic studies is well documented.[10] Without strategies to mitigate litigation it is unlikely that studies of new therapeutics will willingly include these subgroups. This results in a difficult situation for drug developers and clinicians. Although new therapies that achieve FDA approval in reproductive-age women are approved for the same indication in pregnant and lactating women—thus are not used "off label"—without data, professional societies must rely on expert opinion, despite the known limitations, for their guidance.

Given the importance of reducing risk of COVID-19 for pregnant and lactating women and their neonates, it is essential to determine the safety profile of these vaccinations in real time. Capturing data on adverse effects and safety profile is important both to provide the data for women and to provide accurate expectations. The known adverse effects, such as fever, chills, and muscle aches, may concern a pregnant or lactating woman and thus follow-up calls to their clinicians may be essential both for reassurance and to reduce the burden on emergency departments. Rigorously designed studies with proactive data collection to record both vaccine-related symptoms as well as obstetric outcomes will advance current understanding of these events. In addition, women who were pregnant have inadvertently participated in the ongoing trials. It would be helpful if these data were systematically analyzed. As systematic and proactive data on COVID-19 vaccination in pregnant and lactating women are gathered, evidence-based recommendations regarding mRNA vaccination to reduce harms from COVID-19 will replace expert opinion.

COVID-19 causes significant morbidity and mortality, with respiratory illness requiring hospitalization in 5% to 6% of all SARS-CoV-2–infected pregnant women.[1] Given what is known about the COVID-19 vaccines, the limited data regarding COVID-19 vaccines in pregnant and lactating women from those who have been immunized, and use of other vaccines during pregnancy, physicians can empower women to make an informed decision. With an understanding of the important practice of vaccination in pregnancy, the use of other vaccines during pregnancy, the efficacy and safety of COVID-19 mRNA vaccines in nonpregnant populations, and their mechanism of inducing an immune response, clinicians can outline the benefit of prevention of COVID-19 illness, as well as the undefined but possibly limited risk to the fetus, and potential benefit to the neonate. As part of the discussion, clinicians should acknowledge with empathy the limited available evidence, as well as the tension over the potential benefits of vaccination weighed against the potential risks—whether real or theoretical—and be prepared to dispel myths.

ARTICLE INFORMATION

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