

Vaccination of Pregnant Women Against COVID-19

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ABSTRACT

Pregnant women are at increased risk for severe morbidity and mortality following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading some countries to recommend vaccination of pregnant women against coronavirus disease 2019 (COVID-19). These recommendations are based on studies conducted early in the pandemic, and thus, the pregnant women in these studies most likely did not have pre-existing immunity to SARS-CoV-2 at the time of infection. The susceptibility of pregnant women and their infants to SARS-CoV-2 and the severity of infection may be attenuated as the pandemic progresses and an increasing number of women will have pre-existing immunity (following natural infection or vaccination prior to pregnancy) during pregnancy. The reactogenicity, immunogenicity and efficacy of COVID-19 vaccines administered in pregnancy may also be affected by the pre-existing immunity of pregnant women. Maternal vaccine trials should be evaluated in the context of their timing in the pandemic and interpreted based on the pre-existing immunity of pregnant women.

Several coronavirus disease 2019 (COVID-19) vaccines (eg, BNT162b2, mRNA-1273) (1)(2) have received emergency use authorization by the US Food and Drug Administration and have also been approved by regulatory agencies in other countries. The US Centers for Disease Control and Prevention currently recommends that pregnant women may choose to receive a COVID-19 vaccine. (3) Universal vaccination against COVID-19 in pregnancy has been recommended for all pregnant women in some countries.

Unfortunately, pregnant women were not included in the initial vaccines' efficacy trials. (1)(2) It is critical to include and even prioritize pregnant women in early vaccine studies for vaccine-preventable diseases that are of potential concern for pregnant women and/or their infants. Excluding pregnant women from early vaccine studies leads to insufficient data to make evidence-based recommendations, leaving pregnant women excluded from vaccine rollout plans. This makes generation of further evidence very challenging, a situation that was recently termed as a "perpetuated cycle of exclusion." (4)

In addition to the challenges that stem from excluding pregnant women from initial vaccine studies, there are also unique circumstances that are relevant to the consideration of vaccination against COVID-19 during pregnancy, and the interpretation of results of the maternal vaccine studies as the pandemic progresses.

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ABBREVIATIONS

CDC Centers for Disease Control and Prevention
 COVID-19 coronavirus disease 2019
 SARS-CoV-2
 severe acute respiratory syndrome coronavirus 2

THE NEED FOR VACCINATION AGAINST COVID-19 IN PREGNANCY

Vaccination in pregnancy enhances maternal immunity against vaccine-preventable diseases and increases transplacental transfer of vaccine-specific antibodies to the newborn. This strategy aims to protect against infections that are relevant to pregnant women, young infants or both and has been successfully used to protect against pertussis and influenza diseases. (5) The goal for vaccination against influenza is to protect pregnant women and their young infants from influenza disease, while vaccination against pertussis aims to mainly protect young infants from whooping cough disease. (5) The recommendations for the use of these vaccines in pregnancy are supported by studies that showed that influenza disease is severe in pregnant women and young infants and that pertussis is severe in young infants. (6)(7)(8) These studies were conducted during endemic states (i.e. the constant presence of the pathogen in a population) of these diseases.

It is important to define the target for COVID-19 vaccination during pregnancy. Although the absolute risk for severe COVID-19 disease is low among pregnant women, this population is at increased risk for both severe morbidity (e.g. admission to intensive care unit, mechanical ventilation) and mortality following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when compared with non-pregnant women of comparable ages. (9)(10)(11) Infection with SARS-CoV-2 in pregnancy is also associated with higher risk of preterm delivery compared with an uninfected pregnancy. (12)(13) Because these outcome studies were conducted during the early stages of the pandemic, these pregnant women most likely did not have pre-existing immunity to SARS-CoV-2 at the time of infection. As the pandemic progresses, an increasing number of women will enter pregnancy with natural or vaccine-induced immunity to SARS-CoV-2 that was acquired before pregnancy. Thus, the risk of these women to contract SARS-CoV-2 infection during pregnancy and the severity of COVID-19 may be attenuated, as has been observed in the non-pregnant population. (14)

Studies have shown that COVID-19 is uncommon in neonates admitted to the hospital, (15) and that most neonates with SARS-CoV-2 infection are either asymptomatic or have mild symptoms. (16) Infants with COVID-19 have also been shown to have a mild disease. (17)(18) However, although the absolute number of neonatal cases of COVID-19 disease is small, the proportion of neonates admitted to critical care is high (15% [7 out of 40 neonates <1 month with laboratory-confirmed SARS-CoV-2¹⁹] and 32% [17 out of 53 neonates <1

month with laboratory-confirmed SARS-CoV-2]). These data are from studies conducted early in the pandemic, and thus, these newborns and infants were likely born to women immune naïve to SARS-CoV-2. (15)(16)(17)(18)(19)(20) As the pandemic progresses, the susceptibility of newborns and infants to SARS-CoV-2 and risk for severe disease is expected to be directly affected by the levels, function and durability of maternal SARS-CoV-2 antibodies transferred across the placenta to the newborn. Several studies have shown that anti-SARS-CoV-2 antibodies are detected in cord blood of women infected with SARS-CoV-2 in pregnancy. (21)(22)(23) While the clinical significance of these antibodies is difficult to interpret as no correlate of protection has been yet identified for COVID-19, it is plausible that these antibodies will provide some degree of clinical protection. Thus, the risk of newborns and young infants acquiring SARS-CoV-2 infection in infancy and the severity of disease may be attenuated if the infants are born to women with pre-existing immunity acquired before pregnancy (either natural or vaccine-induced).

INTERPRETATION OF COVID-19 VACCINE TRIALS IN PREGNANCY IN RELATION TO PRE-EXISTING IMMUNITY

Studies of the vaccines that have been used in pregnancy (e.g. pertussis and influenza) assessed the reactogenicity, immunogenicity and efficacy of these vaccines in a population of pregnant women that were assumed to have pre-existing immunity to the endemic targeted pathogen, via previous infection and/or prior vaccination. (24)(25)(26)(27)

Pre-existing immunity to SARS-CoV-2 is not assumed due the nature of the pandemic; thus, vaccine trials need to be interpreted according to their timing in the pandemic and pre-existing immunity of pregnant women.

Reactogenicity

As pregnant women were excluded from initial COVID-19 vaccine trials, published data are scarce about the reactogenicity of COVID-19 vaccination in pregnancy. Reactogenicity following vaccination in pregnancy will likely be impacted by pre-existing maternal immunity. In the non-pregnant population, pre-existing immunity has been associated with greater systemic reactions to mRNA COVID-19 vaccine. (28)

Immunogenicity

Current data on the immune response to COVID-19 vaccines in pregnancy is derived mainly from small observational studies. Anti-SARS-CoV-2 antibodies were detected

in cord blood after vaccination with 2 doses of mRNA COVID-19 vaccines in two studies (27 pregnant women)(29) (20 pregnant women). (30) The use of a two-dose regimen aims to prime the immune system with the first dose and later provide a booster with the second dose, and this regimen is important in a host that is immune naïve to SARS-CoV-2. Previous priming will likely impact the quantity and function of antibodies generated after vaccination in pregnancy, with higher levels and function of antibodies expected. In the non-pregnant population, pre-existing immunity to SARS-CoV-2 enhanced vaccine-induced immune responses to a single dose of mRNA COVID-19 vaccine. (28)

Efficacy

Efficacy trials need to demonstrate that vaccination in pregnancy protects against maternal disease during gestation. Efficacy of vaccines will also be affected by pre-existing immunity. Vaccination of an immune-naïve population of pregnant women may demonstrate high vaccine efficacy. However, it is possible that the same degree of vaccine efficacy may not be evident in pregnant women with pre-existing immunity, suggesting that booster vaccination may not augment the protection afforded by pre-existing immunity (following either natural infection or vaccination prior to pregnancy) to the same level observed in naïve populations. (31) The same may also apply to the protection of newborns following vaccination of their mothers in pregnancy.

SAFETY OF VACCINATION AGAINST SARS-COV-2 IN PREGNANCY- PRELIMINARY US DATA

Fortunately, despite the exclusion of pregnant women from early vaccine studies, data on safety of vaccination in pregnancy are accumulating. Recently, preliminary data from three U.S. vaccine safety monitoring systems were published. (32) Local (injection-site pain) and systemic (fatigue,

headache, and myalgia) reactions were the most frequent, but were reported at the same level among non-pregnant women. (32) These reactions were more frequent after the second dose of mRNA COVID-19 vaccines, supporting that pre-existing immunity (following the first vaccine dose) may be associated with higher reactogenicity. Furthermore, the proportions of adverse pregnancy and neonatal outcomes (e.g., fetal loss, preterm birth, neonatal death) were similar to the incidences reported in pregnant women before the pandemic. These data provide further support to the recommendation of vaccination against SARS-CoV-2 in pregnancy.

CONCLUDING REMARKS

The susceptibility of pregnant women and young infants to SARS-CoV-2 may change as the pandemic progresses and the number of pregnant women who enter pregnancy with natural or vaccine-induced immunity will likely increase. The reactogenicity, immunogenicity and efficacy of COVID-19 vaccines may be affected by pre-existing immunity. Therefore, vaccine studies should account for pre-existing immunity in pregnant women.

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- Know the effects on the fetus and/or newborn infant of other maternal infections (eg malaria) and their management.

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