Safety and Benefits of COVID-19 Vaccination in Pregnancy—Implications for the Maternal Vaccination Platform

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The development of safe and effective vaccines against the novel SARS-CoV-2 virus, the cause of COVID-19 pandemic, was justifiably hailed as a major advance in protecting the population against severe and fatal infection. The vaccine rollout was targeted toward recognized communities at risk, including older adults, those with comorbidities, and those who were immunosuppressed.1,2 Pregnant women, and by extension, their infants, were included in these high-risk groups for vaccination.3 The prioritization of pregnant women was justified from historical observations of disproportionate mortality and morbidity during previous influenza pandemics. For example, during the 1918 Spanish influenza pandemic, 50% of infected pregnant women died. Despite advances in public health, intensive care, and therapeutics a century later, during the 2009 H1N1 influenza pandemic, infected pregnant women had a 7-fold higher need of intensive care compared with those who were not pregnant and accounted for 5% of H1N1-associated deaths in the US but only 1% of the population.4,5 Increased COVID-19-related maternal and neonatal morbidity and mortality was observed in international longitudinal observational and prospective cohort studies.6-8 Similar studies demonstrate the immunogenicity, effectiveness, and infant protection conferred by maternal vaccination.8-11 It is, therefore, disappointing that the uptake of COVID-19 vaccination in pregnancy remains suboptimal.11,12

The most compelling factor influencing a pregnant woman’s decision against being vaccinated in pregnancy is concern regarding the safety of the intervention for the infant. In this issue of JAMA Pediatrics, Jorgensen and colleagues provide considerable evidence that this concern is unfounded for COVID-19 vaccination.13 In a well-designed, population-based, retrospective cohort study of live births in Canada, investigators studied 142 006 singleton, live births, 60% of whom had been born to mothers who received 1 or more messenger RNA (mRNA) COVID-19 vaccine doses during pregnancy and compared them with the infants of unvaccinated women. Other studies have assessed short-term neonatal outcomes, but this study attempted to assess a broader range of outcomes and extended follow-up to 6 months of age. In this robust analysis, maternal-infant pairs were linked through the Canadian Mother-Baby (MOMBABY) database that links hospital delivery records (>99% of all births in Ontario) with newborn discharge data. A centralized vaccine registry allowed the investigators to obtain accurate vaccination data, including factors that influence a pregnant woman’s attitude toward (or against) vaccination and their perception of safety such as the timing after a vaccine dose is administered. Variability in intervals between vaccine doses due to vaccine supply constraints were also accounted for through use of this registry. Infant follow-up data to age 6 months were available for 79% of the cohort, and investigators adjusted for multiple covariates that might impact vaccination decisions and infant outcomes such as infant sex, timing of birth, maternal demographics, and risk factors for severe COVID-19 infection, natural COVID-19 infection, and history of seasonal influenza vaccination as a proxy for vaccine acceptance. The reliability and significance of the findings were further strengthened by performing subgroup and sensitivity analyses that accounted for 10 separate factors that might have been confounding factors.

The findings reported by Jorgensen and colleagues13 are striking and reassuring, confirming the benefit of this intervention. The risks of severe neonatal morbidity, neonatal death, and admission to the neonatal intensive care unit were all significantly lower in infants of vaccinated mothers, with an adjusted risk ratio (ARR) of 0.86 (95% CI, 0.83-0.90) for severe neonatal morbidity, an ARR of 0.47 (95% CI, 0.33-0.65) for death, and an ARR of 0.86 (95% CI, 0.83-0.89) for neonatal intensive care unit admission. Infants of vaccinated mothers did not have higher rates of readmission in the neonatal period up to 6 months of age. Results were unaffected by number of vaccine doses, trimester of maternal vaccination, type of mRNA vaccine received, or infant sex. The significance of these findings in this analysis compared with those of other studies lies in the robust number of participants, high vaccination rate of mothers, inclusion of a greater proportion of maternal-infant pairs vaccinated in the first trimester (a period where both pregnant women and health care providers may be hesitant to vaccinate), and duration of infant follow-up. These all combine to provide considerable evidence of the safety of COVID-19 vaccination.

The impact of these robust study results can be applied not only to COVID-19 vaccination but to the benefits of other maternal vaccines currently recommended and those on the horizon.3,12 Safe and effective vaccines such as the COVID-19 vaccine should provide confidence in the maternal vaccination program where maternal vaccines provide protection for mothers and neonates against potentially devastating infections. At the same time, concerns about vaccine adverse effects such as birth defects, spontaneous abortion, preterm labor, and other adverse pregnancy outcomes are not observed.11 Although influenza vaccine has been recommended to protect pregnant persons and their newborns against influenza for decades, vaccination rates in pregnancy hover at approximately 50%.14 Reasons for these poor vaccination rates in-
clude safety concerns despite years of safety data, lack of awareness of risk for severe morbidity and mortality associated with influenza in pregnancy, and lack of knowledge that maternal vaccination protects the newborn when the newborn is most vulnerable before vaccination at 6 months of age. Maternal tetanus, diphtheria, and acellular pertussis vaccine also recommended during each pregnancy has robust safety data while demonstrating excellent protection for infants again when they are most vulnerable to death before 2 months of age.3,4,12 Recent data show that maternal vaccination uptake is low for all recommended vaccines, suggesting that greater efforts are needed to provide education about the harmful effect of these diseases on pregnancy specifically as well as to broadly message the safety data that emerges from real-world use.11,12,14 In initial clinical trials, the maternal respiratory syncytial virus (RSV) vaccine effectively prevents severe and life-threatening RSV infection in neonates through the robust transfer of maternally derived antibodies.15 An RSV vaccine for use in pregnancy has been approved by the US Food and Drug Administration, and recommendations on its use are pending from the Centers for Disease Control and Prevention. Once it is available, mothers and their clinicians will rely on safety and efficacy data generated from the trial and balance these data against their knowledge of the devastating effects of RSV for newborns. Still, gaining confidence leading to increased vaccine uptake will require ongoing review of safety data with real-world use as was provided by Jorgensen et al13 for the COVID-19 vaccine. These important findings should not only provide further impetus to increase vaccination of pregnant persons against COVID-19 infection but also increase confidence that safe and effective maternal vaccines can protect pregnant persons, their newborns, or both.3,12

How then do we encourage vaccination in pregnancy, against COVID-19 infection and other pathogens that threaten the health of mothers and infants? Certainly, studies such as those reported here and others reporting the longitudinal surveillance of safety, immunogenicity, and effectiveness are critical.11-13 Strong partnerships and visible support from trusted organizations such as the World Health Organization and national and professional organizations such as the Centers for Disease Control and Prevention, American College of Obstetricians and Gynecologists, American Academy of Pedia-

REFERENCES


10. Murphy EA, Guzman-Cordozo C, Sukhu AC, et al. SARS-CoV-2 vaccination, booster, and


