COVID-19 mRNA Vaccines During Pregnancy
New Evidence to Help Address Vaccine Hesitancy
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SARS-CoV-2 infection during pregnancy is associated with increased risk for maternal morbidity and adverse birth outcomes.1,2 COVID-19 vaccines are effective for preventing severe disease, including in pregnant populations.3 Although more than 100 countries recommend COVID-19 vaccination during pregnancy,4 COVID-19 vaccination in pregnant people has lagged behind that for age-matched, nonpregnant adults.5,6 As of February 2022, the US Vaccine Safety Datalink estimated that 68% of pregnant individuals have completed the primary COVID-19 vaccine series.6 Persistent wide disparities in COVID-19 vaccination during pregnancy by race or ethnicity are likely to exacerbate longstanding disparities in maternal morbidity and mortality.6

Vaccine hesitancy during pregnancy was understandable when COVID-19 vaccines were first authorized,7 because pregnant people were excluded from the initial COVID-19 vaccine trials. Thus, initial data on pregnancy or birth outcomes after maternal COVID-19 vaccination were limited to inadvertent exposures among trial participants early in pregnancy. The mRNA vaccines were novel and their safety in pregnancy was presumed, but not yet proven. Over the past 14 months, a substantial body of evidence supporting the safety of the mRNA COVID-19 vaccines in pregnancy has accumulated. Observational studies from Norway, Israel, and the US have reported that the mRNA COVID-19 vaccines administered during pregnancy were not associated with increased risk for miscarriage, preterm birth, or other select obstetric and birth outcomes.8–11

In this issue of JAMA, 2 population-based observational retrospective studies evaluating outcomes in more than 250 000 pregnancies from 3 countries together provide the strongest evidence to date regarding the safety of COVID-19 vaccines in pregnancy.12,13

Fell and colleagues12 used data from the Ontario birth registry, linked with the provincial immunization information system, to identify 97 590 pregnancies eligible for COVID-19 vaccination and with an expected delivery date or live birth from December 14, 2020, to September 30, 2021. Of these pregnant individuals, 23% were vaccinated during pregnancy; most were vaccinated in third trimester. Compared with those vaccinated after pregnancy and, in separate analyses, compared with those who were unvaccinated during pregnancy, COVID-19 vaccination during pregnancy was not associated with increased risks for postpartum hemorrhage, chorioamnionitis, cesarean delivery, neonatal care admission, or low Apgar score.

Magnus and colleagues13 used data from the Pregnancy Register in Sweden and the Medical Birth Registry of Norway, linked with vaccine registries from both countries, to identify 157 521 singleton pregnancies from January 1, 2021, through early January 2022 and reaching 22 weeks’ gestation. In this cohort, 18% of participants received a COVID-19 vaccine during pregnancy; the majority were vaccinated in the second or third trimester of pregnancy. Compared with individuals who remained unvaccinated during pregnancy, COVID-19 vaccination during pregnancy was not associated with increased risk for preterm birth, stillbirth, small-for-gestational age, low Apgar score, or neonatal care admission.

Overall, the findings reported by Fell et al12 and Magnus et al13 are extremely reassuring and consistent with published data on more than 40 000 live births in the US (Vaccine Safety Datalink)9 and from nearly 25 000 live births in Israel (Maccabi Healthcare Services).11 Strengths of these studies include the large and well-defined population-based cohorts, the availability of validated data on vaccine exposures and birth outcomes through regional and national registries, and the thoughtful approaches addressing the following common sources of bias in observational studies of maternal vaccination: healthy vaccinee bias and confounding by indication, immortal time bias, and cohort truncation.14,15

Healthy vaccinee bias refers to differences between vaccinated and unvaccinated populations attributed to vaccination, including in their health or health-related behaviors, that can bias toward a protective effect. Confounding by indication occurs when vaccination is more common among those at increased risk for adverse outcomes after vaccination due to underlying comorbidities and can bias observational studies of vaccine safety in the opposite direction as healthy vaccinee bias. In the Ontario cohort in the study by Fell et al and in the Swedish and Norwegian cohorts in the study by Magnus et al, individuals vaccinated during pregnancy were older than those who were not vaccinated during pregnancy.12,13 Magnus et al reported that, compared with unvaccinated individuals, those vaccinated during pregnancy had higher levels of education, whereas Fell et al observed that vaccinated individuals resided in higher-income neighborhoods and were less likely to have obesity, and less likely to report ever smoking.9

To address these potential sources of bias, Magnus et al adjusted analyses for age, parity, and select sociodemographic and clinical factors; Fell et al applied a sophisticated approach to minimize healthy vaccinee bias and confounding.
by indication, using all data available to calculate propensity to be vaccinated. Inverse probability weighting of the propensity to be vaccinated was then applied in adjusted analyses. When groups differ substantially in their health or health-related behaviors, or when data on key differences between groups are not available, a propensity score cannot fully minimize bias. As such, the comparison of individuals vaccinated during pregnancy vs those vaccinated after pregnancy, conducted by Fell et al, was important.12

The investigators used different methods to address immortal time bias, another potential source of bias in observational studies of maternal vaccination. Shorter pregnancies have less time (fewer days) while pregnant to be vaccinated. This bias can be exacerbated when vaccines are only available over a short period or when they are indicated during a limited gestational window. Magnus et al appropriately evaluated vaccination as a time-dependent exposure in relation to preterm birth and stillbirth, and the hazard ratios showed neither an increased risk nor a decreased risk associated with vaccination. In contrast, Fell et al focused on peripartum outcomes, assessed at the time of delivery. Outcomes such as chorioamnionitis, low 5-minute Apgar score, and neonatal care admission were presumed to not be affected by length of pregnancy and thus risk ratios were evaluated using Poisson regression models. Magnus et al similarly used logistic regression to evaluate neonatal care admission and low Apgar score, not accounting for potential time-dependency of the vaccine exposure. Compared with full-term births, low Apgar scores and neonatal care admissions are much more common in preterm births. Thus, it is not surprising that in a cohort of nearly 100,000 births, Fell et al reported a statistically significant “protective” association between COVID-19 vaccination in pregnancy and these outcomes. Although Magnus et al did not report a similar “protective” association in the full cohort, this finding was evident in sensitivity analyses restricted to third-trimester vaccination.

The studies by Fell et al and Magnus et al both included analytic approaches intended to minimize cohort truncation bias, which results from over-selection of pregnancies of shorter or longer intervals based on cohort inclusion criteria. This bias can be avoided by using the expected due date, rather than defining cohort eligibility by the date of birth alone. Fell et al included pregnancies with a birth date or expected due date after the COVID-19 vaccines were introduced in Ontario and excluded individuals who did not have the opportunity to reach 42 weeks’ gestation by the end of the study period, avoiding over-selection of shorter pregnancies. Magnus et al also excluded pregnancies that would not have reached 42 weeks’ gestation by the end of the study period; however, pregnancies at the start of the period with a shorter gestation may have been missed.

Although these studies thoughtfully addressed these common sources of bias, both studies also have limitations. First, there were few first trimester vaccinations in these cohorts. To date, only 1 published study from Israel has described birth outcomes after first-trimester vaccination.11 Second, although the findings regarding maternal COVID-19 vaccination and low Apgar score or neonatal care admission are reassuring, future studies are needed to assess outcomes beyond the immediate perinatal period, including infant morbidity, growth, and development. Third, too few individuals received a viral vector vaccine to comment on the safety of this type of vaccine. Although many countries recommend mRNA vaccines in pregnant populations, others have financial barriers and limited supply. For example, in India, a country with one-sixth of the world’s births, the mRNA vaccines are not currently available and viral vector-based or inactivated virus vaccines are used in pregnancy.4

The reports by Fell et al and Magnus et al, with their large study populations, thoughtful analytic approach, and lack of any suggestion of safety concerns, are reassuring, especially for pregnant individuals with access to mRNA vaccines in their second or third trimester. However, the question remains whether the evidence from these 2 studies will convince those who remain unvaccinated to receive a COVID-19 vaccine during pregnancy. More work is needed to achieve equity in the availability, acceptance, and administration of life-saving interventions such as the COVID-19 vaccine. Studies of vaccine safety during pregnancy, similar to the studies reported in this issue of JAMA, should be replicated in countries or regions where the viral vector vaccine or inactivated vaccine are the primary COVID-19 vaccines used in pregnant populations. Generation of further evidence should be coupled with effective strategies for disseminating evidence regarding the benefits and safety of COVID-19 vaccination during pregnancy.

REFERENCES


