Safety of third SARS-CoV-2 vaccine (booster dose) during pregnancy

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BACKGROUND: COVID-19 during pregnancy is associated with adverse outcomes for both the mother and fetus. SARS-CoV-2 vaccination has significantly reduced the risk for symptomatic disease. Several studies have reported on the safety of SARS-CoV-2 vaccination during pregnancy, with no adverse effects on the obstetrical outcomes. However, data regarding the obstetrical outcomes following a booster dose of the SARS CoV-2 vaccination during pregnancy have not yet to be published.

OBJECTIVE: This study aimed to examine the association between the booster dose of the SARS CoV-2 vaccination during pregnancy and obstetrical outcomes.

STUDY DESIGN: This was a retrospective cohort study of women who delivered between July and October 2021 at a large tertiary medical center. We compared women who received the booster vaccination dose during pregnancy with women who were not vaccinated and with those who only received 2 vaccination doses. Primary outcomes were the incidence of preterm labor and of small for gestational age neonates. Secondary outcomes were other maternal and neonatal complications. A secondary analysis investigating the association between the time from vaccination to delivery and the outcomes was also performed. Multivariable logistic regression models were used to adjust for potential confounders.

RESULTS: There were 6507 women who met the inclusion criteria: 294 women received 3 doses of the vaccination, 2845 women received only 2 doses, and 3368 were unvaccinated. Patients receiving 3 doses of the vaccine were older and more likely to smoke than unvaccinated patients. No differences were noted among the triple-vaccinated, twice-vaccinated, and unvaccinated groups with regards to preterm birth and the incidence of small for gestational age neonates. Regarding the secondary outcomes, women in the triple-vaccinated group had higher rates of postpartum hemorrhage (9.5% vs 3.21%; $P<.001$) and gestational diabetes mellitus (12.2% vs 8.3%; $P=.02$) and were less likely to have hypertensive disorders of pregnancy (0% vs 1.4%; $P=.041$) than the unvaccinated group. Compared with the twice-vaccinated patients, patients with 3 doses of the vaccine were more likely to experience postpartum hemorrhage (9.5% vs 3.5%; $P<.001$) and were less likely to have a low umbilical artery pH (0.7% vs 6.1%; $P<.001$). In the sensitivity analysis comparing patients who delivered within 2 weeks of the third vaccination dose (n=53) with those who delivered at least 6 weeks after vaccination (n=96), there were no differences in the rates of small for gestational age neonates, preterm birth, postpartum hemorrhage, or cesarean delivery.

CONCLUSION: Receiving the booster dose of the SARS-CoV-2 vaccination during pregnancy was not associated with adverse obstetrical outcomes when compared with unvaccinated or twice-vaccinated women. However, higher rates of postpartum hemorrhage were observed. Further studies on a larger scale are needed to confirm these findings.

Key words: booster, outcomes, pregnancy, preterm birth, safety, SARS-CoV-2, small for gestational age, trimester, vaccination

Introduction

With >5 million casualties worldwide, COVID-19 has been a major source of concern for the international medical community.[1]

Evidence suggests that SARS-CoV-2–infected pregnant women are at higher risk for hospitalization and complications, including admission to the intensive care unit and invasive mechanical ventilation, than the general population.[2] Moreover, several studies have reported that COVID-19 during pregnancy is associated with adverse maternal and neonatal outcomes, including preterm birth and small for gestational age (SGA) birthweight.[3,4]

SARS-CoV-2 vaccinations were introduced late in 2020 and have markedly reduced morbidity and mortality in the general population.[5] Although the original clinical trials of the pharmaceutical companies did not include pregnant women, several retrospective studies have reported on the safety of SARS-CoV-2 vaccination during pregnancy, showing pregnancy outcomes that are comparable with the unvaccinated population.[6,7] The first prospective trial to include this high-risk population began early in 2021 (Pfizer BioNTech, ClinicalTrials.gov identifier: NCT04754594) with primary results due to be released in August 2022.[8]

The booster dose (third vaccination dose) was introduced in Israel at the end of July 2021 because of the surge in cases involving the delta variant and the increase in general infection rates.[9]

Individuals were advised to receive the booster dose if ≥5 months had passed since the second vaccination dose. A large trial that included pregnant women found that the boosted population were at a lower risk for developing severe COVID-19–related outcomes.[10]

To the best of our knowledge, the maternal and neonatal outcomes following a booster dose of the SARS CoV-2 vaccination during pregnancy have not yet been published. Therefore, we conducted a retrospective cohort study to examine the association between receipt of the third vaccination dose and adverse obstetrical outcomes.

Materials and Methods

This was a retrospective cohort study conducted at a large tertiary university-

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AJOG MFM at a Glance

Why was this study conducted?

This study aimed to evaluate if receipt of the booster dose of the SARS-CoV-2 vaccination during pregnancy is related to adverse maternal and neonatal outcomes.

Key findings

The neonates born to triple-vaccinated pregnant women did not suffer from adverse outcomes when compared with those born to unvaccinated women. Regarding maternal outcomes, higher rates of postpartum hemorrhage (PPH) were demonstrated in vaccinated women (adjusted odds ratio [aOR], 3.88; 95% confidence interval [CI], 2.41−6.25). In a secondary analysis comparing women who received 3 vaccine doses with those who received 2, there were no considerable differences between the groups in terms of preterm labor or the rate of small for gestational age neonates.

Nevertheless, the rate of low umbilical artery pH (<7) was lower in the triple-vaccinated group (aOR, 0.11; 95% CI, 0.027−0.45). Regarding the maternal outcomes, as found in the primary analysis, the rate of PPH was higher in the triple-vaccinated group (aOR, 3.34; 95% CI, 2.07−5.39).

What does this add to what is known?

This cohort study has provided reassuring information regarding the safety of the booster dose of SARS-CoV-2 vaccination during pregnancy.

affiliated hospital. The study group included women with a singleton pregnancy who received the booster vaccination dose during pregnancy and who delivered in the period from July 2021 to October 2021. The control group included women with a singleton pregnancy who were not vaccinated. As a secondary analysis, we also compared women who received the booster dose during pregnancy with those who only received 2 vaccination doses. Exclusion criteria included multiple pregnancy, COVID-19 infection during or before pregnancy, or unknown timing of vaccination. During the study period, the vaccinations used in Israel were either the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccine.

Clinical and obstetrical data were collected, including maternal age, body mass index (BMI), obstetrical history, and smoking status. The co-primary outcomes were preterm birth, defined as birth before 37 weeks' gestation, and the incidence of SGA neonates, defined as birthweight below the 10th percentile for gestational age and sex using local birthweight standards.[11] Secondary outcomes included gestational diabetes mellitus, mode of delivery, hypertensive disorders of pregnancy, postpartum hemorrhage (PPH), intrauterine fetal demise, 5-minute Apgar score, and umbilical arterial pH and base excess. Gestational age was assigned based on the first trimester ultrasound. Gestational diabetes mellitus was diagnosed using the 2-step test with the Carpenter-Coustan criteria for the 100-g glucose tolerance test.[12] Hypertensive disorders of pregnancy were also defined using the criteria of the American College of Obstetricians and Gynecologists. PPH was defined as an estimated blood loss of >500 mL for a vaginal delivery or >1000 mL for a cesarean delivery.

Descriptive statistics, including medians and interquartile ranges (IQRs), are presented for the obstetrical and clinical covariates. Comparisons were made between patients who received the third vaccine dose and unvaccinated patients and between those who received the third dose and those who received 2 doses. Variables were checked for normality using the Kolmogorov-Smirnov test. Continuous variables were compared using either the *t* tests or the Mann-Whitney *U* test as appropriate. Categorical variables were compared using chi-square or Fisher exact tests.

To assess the potential association between the booster vaccine dose and the outcomes, a multivariable logistic regression was performed. Potential confounders, including maternal age, BMI, nulliparity, and smoking, were added to the model. In addition, we performed a sensitivity analysis to address the timing between vaccination and delivery. We compared the outcomes of patients who delivered within 2 weeks of the third vaccine with those who delivered >6 weeks after receipt of the third vaccine dose. Analysis was performed in Stata 14 (StataCorp, College Station, TX). The study was approved by the local institutional review board (approval number HMO-21-0342).

Results

There were 294 women in the study group. They were compared with a control group of 3368 unvaccinated women and 2845 women who only received 2 vaccine doses. The median gestational age at the time of administration of the third vaccination dose was 34.9 weeks (range, 23−40; IQR, 32.5−37.0). The median time from receipt of the third vaccine dose to delivery was 4.5 weeks (IQR, 2.7−6.9). Patients who received 3 vaccine doses were older and more likely to smoke than unvaccinated patients (Table 1). Patients who had received 3 vaccine doses were slightly older than patients who had received only 2 doses, but they did not differ markedly otherwise (Table 2).

The obstetrical outcomes for triple-vaccinated patients in comparison with unvaccinated patients are shown in Table 1. No differences were noted between the triple-vaccinated and unvaccinated groups with regards to the incidence of preterm birth and SGA neonates. Regarding the secondary outcomes, women in the triple-vaccine group had higher rates of PPH (9.5% vs 3.21%; *P*<.001) and gestational diabetes mellitus (12.2 vs 8.3 %; *P*=.02) and were less likely to have hypertensive disorders of pregnancy (0% vs 1.4%; *P*=.041). A multivariable logistic regression demonstrated that women in the vaccinated

TABLE 1
Baseline characteristics and outcomes of women who received 3 vaccine doses vs unvaccinated patients

Characteristics	Triple vaccinated n=294	Unvaccinated n=3368	*P* value
Maternal age (y)	32 (28−38)	30 (26−34)	<.001
Body mass index (kg/m^2)	27.6 (19.5−27.6)	25.7 (22.2−29.4)	.43
Parity	1 (1−3)	2 (0−3)	.36
Nulliparous	68 (23.1)	850 (25.4)	.42
Smoking	16 (5.4)	89 (2.6)	.006
Primary outcomes			
Preterm birth	14 (4.8)	233 (6.9)	.16
Small for gestational age	20 (6.8)	235 (7.0)	.91
Secondary outcomes			
Gestational age at delivery (wk)	39.6 (38.6−40.4)	38.7 (38.6−40.3)	.35
Cesarean delivery	53 (18.3)	558 (16.6)	.52
Postpartum hemorrhage (>500 mL)	28 (9.5)	108 (3.21)	<.001
Hypertensive disorder of pregnancy	0 (0)	47 (1.4)	.041
Gestational diabetes mellitus	36 (12.2)	278 (8.3)	.019
Intrauterine fetal demise	0 (0)	27 (0.8)	.12
Birthweight (g)	3300 (3025−3600)	3250 (2940−3570)	.18
Apgar 5 min	10 (10−10)	10 (10−10)	.45
5-min Apgar score <7	2 (0.7)	57 (1.7)	.19
Umbilical arterial pH[a]	7.28 (7.22−7.34)	7.29 (7.24−7.35)	.11
Umbilical pH <7.1[a]	2 (2.13)	50 (2.8)	.72
Umbilical arterial base excess[a]	−4.2 (−5.8 to −2.6)	−3.7 (−5.4 to −2.4)	.47

Numbers are reported as the median (interquartile range) or number (percentage).

[a] Umbilical arterial pH and base excess values available for 94 patients in the triple-vaccinated group and for 1814 patients in the unvaccinated group.

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group had a nearly 4 times greater risk for PPH after delivery than the unvaccinated group (adjusted odds ratio [aOR], 3.88; 95% confidence interval [CI], 2.41−6.25). Other parameters assessed within the logistic regression model were not statistically significant (Table 3).

Compared with double-vaccinated patients, patients with 3 vaccine doses were more likely to experience PPH (9.5% vs 3.5%; *P*<.001) and were less likely to have a low umbilical artery pH (0.7% vs 6.1%; *P*<.001) (Table 2). There was no association between having received 3 vaccine doses and either of the co-primary outcomes. In the multivariable logistic regression (Table 4), the following 2 secondary outcomes remained significant: low umbilical artery pH (aOR, 0.11; 95% CI, 0.027−0.45) and PPH (aOR, 3.34; 95% CI, 2.07−5.39). However, umbilical artery gas information was only available for 94 (32%) of the triple-vaccinated patients and for 1616 (57%) of the double-vaccinated patients.

In the sensitivity analysis comparing patients who delivered within 2 weeks of the third vaccine receipt (n=53) with those who delivered at least 6 weeks after receipt (n=96), there were no differences in the rates of SGA, preterm birth, PPH, or cesarean delivery.

Comment

Principal findings

In this study, we reported on the obstetrical outcomes following administration of the booster SARS-CoV-2 vaccination dose during pregnancy. No increase in the rates of preterm birth or SGA neonates was demonstrated among patients who received 3 vaccine doses when compared with women who were not vaccinated or with those who only received 2 vaccine doses. There was, however, a higher rate of PPH in the triple-vaccinated group, although the potential mechanism that may underlie this association is unclear. In addition, we found that the incidence of low (<7.1) umbilical artery pH was lower in the triple-vaccine group than in the double-vaccine group, however, data regarding this variable were only available for a few patients.

Results in the context of what is known

Our findings correlate with the growing amount of evidence showing that the SARS-CoV-2 vaccination is safe to administer during pregnancy. One recent study reported that 2305 women who were vaccinated during pregnancy showed no increase in maternal and neonatal adverse events when compared with unvaccinated women.[13] In another study, Blakeway et al[14] presented data on 1328 pregnant women of whom 140 received at least 1 dose of the SARS-CoV-2 vaccine during pregnancy. No adverse maternal or neonatal outcomes were found in the vaccinated group.

Clinical implications

To date, the question of safety of the booster SARS-CoV-2 vaccine dose during pregnancy has yet to be addressed. Recent studies found that early vaccination during pregnancy was associated with antibody waning throughout pregnancy.[15] Those who received a third dose were found to have markedly higher maternal and neonatal antibody levels.[15,16] These studies support the value of our objective. We found that women who received the booster vaccine dose during pregnancy did not suffer from adverse maternal or neonatal outcomes.

TABLE 2
Baseline characteristics and outcomes of women who received 3 vaccine doses vs those who received 2 doses

Characteristics	Triple vaccinated n=294	Double vaccinated n=2845	*P* value
Maternal age (y)	32 (28–38)	30 (26–34)	<.001
Body mass index (kg/m^2)	27.6 (19.5–27.6)	25.7 (22.7–29.1)	.29
Parity	1 (1–3)	1 (0–3)	.66
Nulliparous	68 (23.1)	757 (26.6)	.20
Smoking	16 (5.4)	97 (3.4)	.08
Primary outcomes			
Preterm birth	14 (4.8)	207 (7.3)	.11
Small for gestational age	20 (6.8)	197 (6.9)	.94
Secondary outcomes			
Gestational age at delivery (wk)	39.6 (38.6–40.4)	39.6 (38.6–40.3)	.87
Cesarean delivery	53 (18.3)	493 (17.3)	.76
Hypertensive disorder of pregnancy	0 (0)	32 (1.1)	.068
Gestational diabetes mellitus	36 (12.2)	264 (9.3)	.10
Postpartum hemorrhage (>500 mL)	28 (9.5)	99 (3.5)	<.001
Intrauterine fetal demise	0 (0)	20 (0.7)	.15
Birthweight (g)	3300 (3025–3600)	3250 (2940–3570)	.25
Apgar 5 min	10 (10–10)	10 (10–10)	.15
5-min Apgar score <7	2 (0.7)	49 (1.2)	.18
Umbilical arterial pH[a]	7.28 (7.22–7.34)	7.28 (7.21–7.35)	.96
Umbilical pH <7.1[a]	2 (0.7)	172 (6.1)	<.001
Umbilical arterial base excess[a]	−4.2 (−5.8 to −2.6)	−4.0 (−5.8 to −2.6)	.77

Numbers are reported as median (interquartile range) or number (percentage).

[a] Umbilical artery gas information was only available for 94 (32%) of the triple-vaccinated patients and for 1616 (57%) of the double-vaccinated patients.

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Research implications

With the continuing COVID-19 pandemic on the one hand and the waning of the immune response over time after administration of the SARS-CoV-2 vaccine on the other hand, there is a need to evaluate the maternal and neonatal outcomes of additional vaccine doses during pregnancy. Our study provides a glimpse into this topic, although larger-scale studies need to be done to confirm our findings.

Strengths and limitations

The main strength of our study is its originality. We report on the neonatal outcomes of women who received the booster dose of the SARS-CoV-2 vac-

TABLE 3
Adjusted odds ratios and 95% confidence intervals for outcomes among the triple-vaccinated and unvaccinated patients

Outcome	Triple vaccinated	Unvaccinated
Preterm birth	0.67 (0.37–1.23)	Ref
Small for gestational age	1.10 (0.68–1.82)	Ref
Cesarean delivery	1.04 (0.75–1.46)	Ref
Postpartum hemorrhage (>500 mL)	3.88 (2.41–6.25)	Ref
5 min Apgar <7	0.27 (0.04–1.98)	Ref
Umbilical pH <7.1	0.92 (0.22–3.92)	Ref

Odds ratios adjusted for nulliparity, maternal age, body mass index, gestational diabetes mellitus, and maternal smoking.

Ref, reference interval.

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TABLE 4
Adjusted odds ratios and 95% confidence intervals for outcomes among the triple-vaccinated and double-vaccinated patients

Outcome	Triple vaccinated	Double vaccinated
Preterm birth	0.61 (0.33–1.11)	Ref
Small for gestational age	1.20 (0.72–2.00)	Ref
Cesarean delivery	1.04 (0.75–1.45)	Ref
Postpartum hemorrhage (>500 mL)	3.34 (2.07–5.39)	Ref
5 min Apgar <7	0.24 (0.033–1.77)	Ref
Umbilical pH <7.1	0.11 (0.027–0.45)	Ref

Odds ratios adjusted for nulliparity, maternal age, body mass index, gestational diabetes mellitus, and maternal smoking.

Ref, reference interval.

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cine during pregnancy. Furthermore, we were able to compare the study group with both vaccinated and unvaccinated women, allowing for a better understanding of the specific effects of the booster dose.

Apart from its retrospective design, this study has several limitations. The women in our study group were older and had a higher incidence of smokers than the unvaccinated group—perhaps confounding our results. Second, we did not have information on the immediate adverse reactions following vaccination. Finally, we were missing data on potential confounders including a history of preterm birth.

Conclusion

Administration of the booster dose of the SARS-CoV-2 vaccine during pregnancy was not associated with adverse obstetrical outcomes when compared with unvaccinated or double-vaccinated women. However, higher rates of PPH were observed. Further studies on a larger scale are needed to confirm this finding. ■

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