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CLINICAL ARTICLE

Obstetrics

Safety of COVID-19 vaccination in pregnant women: A study of the adverse perinatal outcomes

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Abstract

Objective: To compare adverse perinatal outcome among coronavirus disease 2019 (COVID-19)–vaccinated and –unvaccinated pregnant women.

Method: Retrospective equivalence cohort study comparing 930 women who received at least one BNT162b2 (Pfizer/BioNTech) COVID-19 vaccine during the second or third trimester of pregnancy and 964 unvaccinated women. The primary outcome was a composite adverse perinatal outcome including at least one of the following: preterm delivery <35 weeks of gestation, intrauterine fetal death >23 weeks of gestation, intrauterine growth restriction defined as birth weight < 10th percentile, 5-min APGAR score ≤ 7, and neonatal care unit admission.

Results: The authors found no effect of the COVID-19 vaccine on the rate of the individual adverse perinatal outcomes. At least one adverse perinatal outcome was found in 108 (11.25%) of unvaccinated women versus 82 (8.82%) of vaccinated pregnant women ($P = 0.080$). The observed proportion difference (unvaccinated minus vaccinated) was 0.024. In the equivalence analysis with a margin of 0.05, the 90% confidence interval (0.01–0.05) was entirely within the equivalence zone (−0.05 to 0.05) with a P value of 0.032.

Conclusion: The present study demonstrated an equivalent rate of adverse perinatal outcomes among vaccinated and unvaccinated women, thus supporting vaccine safety during the second and third trimesters of pregnancy. The authors believe this information is useful in counseling pregnant women regarding COVID-19 vaccination during pregnancy.

KEYWORDS
adverse perinatal outcomes, coronavirus disease, counseling, COVID-19 vaccine, equivalent study, mRNA, pregnancy, vaccination safety

1 | INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) during pregnancy can potentially lead to more severe disease[1] and has been suggested to increase the risk for preterm birth, cesarean section, and preeclampsia.[2] Data regarding the safety and efficacy of the COVID-19 vaccines in pregnant women, fetus, and neonate are scarce,[3] mainly attributable to the exclusion of pregnant women from clinical vaccine trials.[4]

Because of the potential severity of the disease in pregnant women, the American College of Obstetricians and Gynecologists (ACOG),[5] in collaboration with the Centers for Disease Control and Prevention

(CDC),[6] the Israeli Ministry of Health and the Israel Obstetrics and Gynecology associations,[7] recommend that pregnant women receive a COVID-19 vaccination. However, it was advised that pregnant women be provided with a balanced and clear assessment of their risk of COVID-19 in pregnancy, along with a summary of the potential benefit of COVID-19 vaccines, while acknowledging the limited safety data.[8] Goldshtein et al. demonstrated that severe acute respiratory syndrome coronavirus (SARS-CoV-2) messenger RNA (mRNA) vaccination in pregnant women was associated with a significantly lower risk of COVID-19 infection compared with unvaccinated women.[9] Moreover, the rate of obstetrical complications, including uterine contractions, vaginal bleeding, and premature rupture of membranes, were reported to be extremely low following vaccination.[10] Still, many pregnant women refuse to be vaccinated with the COVID-19 vaccines because of a lack of data on this vaccine safety during pregnancy.[11] Although the COVID-19 vaccine clearly reduces the risk of being infected with a life-threatening virus, as long as the risks to the fetus are unknown, an informed woman's choice should be honored.[12]

Data regarding perinatal outcome following the COVID-19 vaccination is still limited. Self-reported pregnancy outcome among 827 pregnant participants in a vaccination surveillance system was similar to historic controls before the COVID-19 pandemic including preterm birth and small for gestational age.[13] Another small cohort study found no significant difference in adverse pregnancy outcomes between 133 women who received at least one vaccine dose and 399 unvaccinated pregnant women.[14]

Data regarding adverse perinatal outcomes following COVID-19 vaccination is crucial for adequate counseling of pregnant women in their decision on obtaining the vaccine. Thus, our aim was to examine whether the risk for adverse perinatal outcome was equivalent among vaccinated and unvaccinated pregnant women. Our hypothesis was that adverse perinatal outcome in vaccinated pregnant women will be equivalent (i.e., noninferior and nonsuperior) to those of women who did not receive the COVID-19 vaccine during their pregnancy.

2 | METHODS

This was a retrospective cohort study. The study was approved by the institutional review board of Carmel Medical Center (protocol number 0040-17-CMC). The Israeli Ministry of Health issued a recommendation for COVID-19 vaccination with the BNT162b2 (Pfizer/BioNTech) vaccine during pregnancy on January 19, 2021.[7] Therefore, the study included data from all women with a singleton pregnancy over 23 weeks of gestation, admitted to the delivery room of Carmel Medical Center, Haifa, Israel from February 1, 2021, to July 31, 2021. Women with multiple gestations and those who underwent termination of pregnancy were excluded from the study.

Data were collected from the computerized medical records of Carmel Medical Center on the following parameters: maternal data including age, smoking status, maternal self-reported prepregnancy weight and height, and vaccination status including number of COVID-19 vaccine doses received (all vaccinated women in the study received the BNT162b2 vaccine); obstetric history including parity and previous cesarean sections; and course of current pregnancy and delivery including gestational diabetes, intrauterine fetal death (IUFD), gestational age at birth, intrapartum fever above 38°C, delivery mode and neonatal sex, weight, APGAR score, and neonatal intensive care unit (NICU) admission.

The rate of adverse perinatal outcome is relatively low among singleton births in Israel. Thus, our primary outcome was a composite adverse perinatal outcome, which included at least one of the following outcomes: preterm delivery, defined as gestational age at birth <35 weeks; IUFD, defined as fetal death after 23 weeks of gestation; intrauterine growth restriction (IUGR), defined as birth weight < 10th percentile for gestational age and sex according to Dolberg et al. birth weight standards in Israel[15]; 5-min APGAR score ≤ 7; and NICU admission. Secondary outcomes were each of the independent adverse perinatal outcomes; intrapartum fever above 38°C; mode of delivery; low birth weight, defined as birth weight < 2500 g; and macrosomia, defined as birth weight > 4000 g.

2.1 | Statistical analysis

Based on our units' previous data, we estimated the risk for composite adverse neonatal outcome would be 9% to 10% in the unvaccinated women. For sample size calculation, a 2% absolute difference in the rate of adverse outcome was considered clinically significant. Using a two-sided test with a significance level of 5% and 80% power, a sample size of 1784 to 1936 was required.

In order to compare maternal characteristics and birth outcomes between unvaccinated and vaccinated pregnant women, χ^2 test for categorical variables and either *t* test or Mann–Whitney rank test for continuous variables were used. All data were tested for normal distribution (Kolmogorov–Smirnov test) and all tests were two-sided. For comparing the proportions in adverse perinatal outcome, we applied an equivalence analysis for proportion differences based on the Farrington-Manning method with a margin of 0.05. *P* values <0.05 were considered statistically significant.

Analyses were conducted using SigmaPlot for Windows version 11.0 (Systat Software Inc.), Minitab version 16.2.2 (Minitab Inc) and SAS statistical software version 9.4 (SAS Institute Inc).

3 | RESULTS

A total of 1894 women were identified, of which 51 received one dose of the BNT162b2 COVID-19 vaccine, 879 received two BNT162b2 COVID-19 vaccines, and 964 were not vaccinated at the time of birth. Patients were vaccinated during the second or third trimester of their pregnancy. Since only 51 (5.5%) of all 930 vaccinated women received only one vaccine dose prior to delivery, and there were no significant differences between women who received either one or two vaccine doses (data not shown), women who received at least one vaccine dose were considered vaccinated and were compared with unvaccinated pregnant women.

There were no statistically significant differences between vaccinated and unvaccinated pregnant women in any maternal characteristics or birth outcomes (Table 1). This study found no significant effect of the COVID-19 vaccine on the rate of the individual adverse perinatal outcomes including preterm delivery <35 weeks, IUFD, IUGR, 5-min APGAR score of ≤7, and rate of NICU admission (Table 2).

There were two cases of IUFD in the vaccinated group, both low-risk primigravida women. In one case, true umbilical knot was found after the delivery. There were three cases of IUFD in the unvaccinated group. In two cases, fetal malformations and IUGR were suspected during pregnancy without further evaluation. The third case occurred in a woman with cystic fibrosis, cystic fibrosis–related diabetes, and partial protein S deficiency.

At least one adverse perinatal outcome was found in 108 (11.25%) unvaccinated women versus 82 (8.82%) of vaccinated pregnant women ($P = 0.080$). The observed proportion difference (unvaccinated minus vaccinated) was 0.0243. In the equivalence analysis with a margin of 0.05, the 90% confidence interval (0.01–0.05) was entirely within the equivalence zone (−0.05 to 0.05) with a P value of 0.032. Thus, we can declare that the rate of adverse perinatal outcomes in pregnant women vaccinated against COVID-19 was equivalent to unvaccinated women.

4 | DISCUSSION

This study demonstrates that the rate of the composite adverse perinatal outcome was equivalent between vaccinated and unvaccinated pregnant women. Also, when compared with unvaccinated parturients, no significant differences were found in the rate of the composite perinatal outcome or in the individual adverse perinatal outcomes including preterm delivery <35 weeks, IUFD, IUGR, 5-minute APGAR score of ≤7, or the rate of NICU admission.

To date several groups published their findings regarding pregnancy outcome in pregnant women with and without COVID-19 vaccination during pregnancy. No study was randomized or controlled and most were small and retrospective. Similar to our findings, Goldshtein et al. reported no notable differences between the vaccinated and unvaccinated groups regarding IUGR, IUFD, and preterm birth <37 weeks.[9] However, their study design did not provide adequate power to statistically assess differences in adverse events.[9]

Theiler et al., in a paper that was published online prior to a peer-review, compared 140 women vaccinated in their third trimester of pregnancy with 1862 unvaccinated pregnant women (212 of them had experienced a COVID-19 infection during the current pregnancy). They found no significant difference between vaccinated and unvaccinated pregnant women in their severe composite adverse outcome that included both maternal and neonatal complications or in any individual maternal or delivery outcomes.[16] The results of Blakeway et al. are also in agreement with ours, showing similar rates of IUFD, intrapartum fever, cesarean section, small for gestational age, and NICU admissions, when they compared 141 vaccinated pregnant women with 1187 unvaccinated pregnant women.[14] In their study, 86% and 14% were vaccinated in the third and second trimester, respectively.[14] Shimabukuro et al., in a study based on data from the v-safe after vaccination registry, found that adverse neonatal outcomes including preterm birth before 37 weeks, and small size for gestational age (below 10th percentile for gestational age and infant sex) in vaccinated pregnant women were similar to incidences reported

TABLE 1 Maternal characteristics and birth according to vaccination status

	Vaccinated women ($n = 930$)	Unvaccinated women ($n = 964$)	P value
Maternal age (years)	32.0 (29.0–35.0)	31.0 (28.0–35.0)	0.090
Body mass index (kg/m$^{2)}$	27.3 (25.0–30.3)	27.8 (25.0–31.0)	0.127
Smoking	18 (1.9)	24 (2.5)	0.394
Previous cesarean section	123 (13.2)	129 (13.4)	0.920
Primipara	335 (36.0)	357 (37.0)	0.648
Gestational diabetes	58 (6.2)	60 (6.2)	0.991
Gestational age at birth (weeks)	39.6 (38.7–40.3)	39.7 (38.7–40.4)	0.148
Intrapartum fever ≥38°C	11 (1.2)	11 (1.1)	0.932
Delivery mode			
Spontaneous vaginal delivery	672 (72.2)	699 (72.5)	0.992
Vacuum delivery	36 (3.9)	37 (3.8)	
Cesarean section	222 (23.8)	228 (23.6)	
Neonatal female sex	442 (47.5)	440 (45.6)	0.411
Birthweight (g)	3275.0 (2990–3595)	3305.0 (3033–3625)	0.129
Birthweight ≤2500 g	43 (4.6)	43 (4.5)	0.865
Birthweight ≥4000 g	52 (5.6)	72 (7.5)	0.099

Note: Values are expressed as number (percentage) or median (interquartile range).

TABLE 2 Adverse perinatal outcomes according to vaccination status

	Vaccinated women ($n = 930$)	Unvaccinated women ($n = 964$)	*P* value
Preterm delivery <35 weeks	12 (1.3)	15 (1.6)	0.626
Intrauterine fetal death, *n* (%)	2 (0.2)	3 (0.3)	0.681
Intrauterine growth restriction[a]	40 (4.3)	51 (5.3)	0.314
5-minute APGAR score ≤ 7	7 (0.8)	13 (1.4)	0.202
NICU admission	43 (4.6)	63 (6.5)	0.070
Composite adverse perinatal outcome[b]	82 (8.8)	108 (11.2)	0.080

Note: Values are expressed as number (percentage).

[a]Birth weight < 10th percentile according to Dolberg et al.[15]

[b]Composite adverse composite adverse perinatal outcome including at least one of the following outcomes: preterm delivery <35 weeks, intrauterine fetal death, intrauterine growth restriction, 5-minute APGAR score ≤ 7, and neonatal intensive care unit (NICU) admission.

in studies involving pregnant women that were conducted before the COVID-19 pandemic.[13] In another study based on digital questionnaire responses of 57 women who were vaccinated during pregnancy, neonatal outcomes were comparable to the general pregnant population, but no comparison was made with unvaccinated pregnant women.[10] Therefore, all of the studies published thus far show that COVID-19 vaccination during pregnancy did not increase the risk for adverse maternal or neonatal outcomes.

Both Goldshtein et al. and Theiler et al. found that pregnant women who received the BNT162b2 mRNA vaccine during pregnancy had significantly lower risk of COVID-19 infection,[9,16] further supporting the importance of this vaccination during the COVID-19 epidemic.

In our population, we found no statistically significant differences in maternal characteristics between vaccinated and unvaccinated pregnant women. However, Theiler et al. found older age, higher education level, and lower prepregnancy body mass index to be significantly associated with increased likelihood of vaccination, whereas smoking and higher gravity were associated with lower likelihood of vaccination.[16] Blakeway et al. found higher vaccine uptake in women with prepregnancy diabetes and reduced vaccine uptake among the most deprived women.[14]

One of our study's strengths is that we were able to compare birth outcomes of vaccinated and unvaccinated pregnant women during the same time period and both groups were of similar size. Another strength of the current study is that in order to overcome the relatively low rates of adverse perinatal outcomes in the general population in Israel, we built a composite adverse outcome measure. Our data show a slightly insignificant lower rate of adverse perinatal outcomes among vaccinated pregnant women compared with unvaccinated women. The equivalence analysis we applied confirmed our hypothesis that pregnancy outcomes among COVID-19–vaccinated women were as good as in unvaccinated pregnant women. Additionally, as opposed to previous studies,[13,14,16] our study included women vaccinated both in the second trimester and in the third trimester of pregnancy, therefore improving the generalization of the conclusion. The data in this study were taken from primary medical records, and therefore are less likely to be subject to recall bias compared with other studies,[10,13] which were based on questionnaires or participant-reported surveys.

A limitation of our study is the retrospective data acquisition method and its cohort design, exposing it to potential unmeasured confounders. The lack of randomization may lead to differences in the probability of participants being vaccinated and their probability of experiencing the outcome, resulting in possible confounding bias.[17] Unfortunately, we did not have data about possible COVID-19 infections during or prior to their pregnancy in women in the unvaccinated group (there was no recommendation to vaccinate pregnant women with prior COVID-19 infection). Such information had confounding potential. Our study did not include women vaccinated in the first trimester since these women's pregnancies were still ongoing at the time of the study. Therefore, we could not assess adverse outcomes that may occur after exposures earlier in pregnancy such as congenital anomalies or abortions.

5 | CONCLUSION

Our study found an equivalent rate of adverse perinatal outcomes among women who received the COVID-19 vaccine and those who did not, and therefore contributes significant support to vaccine safety during the second and third trimesters of pregnancy. We believe this information could be useful in counseling and encouraging pregnant women regarding the COVID-19 vaccination during pregnancy. Future prospective randomized controlled trials are best to evaluate the safety and perinatal outcomes following COVID-19 vaccination in pregnancy including after first-trimester administration. In the absence of such studies, that might not be feasible or even ethical. We believe that our data add in reassuring pregnant women and their caregivers regarding vaccine safety during pregnancy.

AUTHOR CONTRIBUTIONS

Nir Kugelman: conception of the study, design of the study, methodology, investigation, data analysis, manuscript writing/editing, project administration. Arieh Riskin: investigation, data analysis, methodology, manuscript writing/editing. Reuven Kedar: manuscript writing/editing, supervision, project administration. Shlomit Riskin-Mashiah: conception of the study, design of the study, methodology, investigation, data analysis, manuscript writing/editing, project administration.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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