Obstetric and Early Neonatal Outcomes Following Second and Third COVID-19 Vaccination in Pregnancy

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ABSTRACT **Background**: Pregnant women are at higher risk for severe coronavirus disease 2019 (COVID-19). Since the release of the BNT162b2 messenger RNA vaccine (Pfizer/BioNTech), there has been accumulated data about the three vaccine doses. However, information regarding obstetric and neonatal outcomes of pregnant women vaccinated with the third (booster) vaccine is limited and primarily retrospective.

Objectives: To evaluate the obstetric and early neonatal outcomes of pregnant women vaccinated during pregnancy with the COVID-19 booster vaccine compared to pregnant women vaccinated only by the first two doses.

Methods: We conducted a cross-sectional study of pregnant women who received the BNT162b2 vaccine during pregnancy. Obstetric and neonatal outcomes were compared between pregnant women who received only the first two doses of the vaccine to those who also received the booster dose.

Results: Overall, 139 pregnant women were vaccinated during pregnancy with the first two doses of the vaccine and 84 with the third dose. The third dose group received the vaccine earlier during their pregnancy compared to the two doses group (21^2 vs. 31^5 weeks, respectively, $P < 0.001$). No differences in obstetric and early neonatal outcomes between the groups were found except for lower rates of urgent cesarean delivery in the third dose group (adjusted odds ratio 0.21; 95% confidence interval 0.048–0.926, $P = 0.039$).

Conclusions: Compared to the first two doses of the BNT162b2 vaccine given in pregnancy, the booster vaccination is safe and not associated with an increased rate of adverse obstetric and early neonatal outcomes.

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KEY WORDS: BNT162b2 vaccine (Pfizer/BioNTech), coronavirus disease 2019 (COVID-19), neonatal outcome, obstetric outcome; prenatal vaccination

Pregnant women are at higher risk for severe coronavirus disease 2019 (COVID-19) illness, including hospitalization, mechanical ventilation, and death, compared to non-pregnant women [1]. Data regarding COVID-19-related pregnancy outcomes are still under dispute. Several studies demonstrated increased preterm birth, pre-eclampsia, and stillbirth rates among pregnant women infected with COVID-19, although some research has suggested that the increased risk may be limited to individuals with severe COVID-19 infection [2].

Since the release of the BNT162b2 messenger RNA vaccine (Pfizer/BioNTech), accumulated data about the first two doses given during pregnancy have shown reassuring results regarding its safety in terms of adverse events and adverse obstetric and neonatal outcomes, and efficacy in preventing severe illness [3-6]. However, the reduced efficacy of the BNT162b2 vaccine over time and the emergence of two additional outbreaks in Israel, Delta (B.1.617.2) variant in July 2021 and the Omicron (BA.1) variant in December 2021 [7], led the Israel Ministry of Health to recommend a third (booster) vaccination for high-risk populations including pregnant women. Studies showed that both Delta and Omicron infections in unvaccinated pregnant women were associated with higher rates of adverse pregnancy outcomes.

Studies assessing the third dose given in pregnancy have shown similar results to the first two doses of the BNT162b2 vaccine in terms of safety profile and efficacy in decreasing infection rate and severe illness [8,9] as well as generating a significant maternal humoral immune response [10]. However, information regarding obstetric and neonatal outcomes of pregnant women vaccinated with the third (booster) vaccine [11,12] is limited and primarily retrospective.

With this cross-sectional study, we evaluated the obstetric and early neonatal outcomes of pregnant women vaccinated during pregnancy with the third (booster) vac-

cine compared to pregnant women vaccinated only with the first two doses.

PATIENTS AND METHODS

STUDY DESIGN AND PARTICIPANTS

This cross-sectional study of pregnant women was conducted at two different timeframes. The first was between December 2020 and March 2021 and included pregnant women vaccinated only with the first two doses of the BNT162b2 vaccine during pregnancy. The second was between August 2021 and January 2022 and included pregnant women vaccinated with the third (booster) dose of the BNT162b2 vaccine during pregnancy. This group of vaccinated women was defined as pregnant women who received the third (booster) dose of the BNT162b2 during pregnancy and completed the first two doses at least 5 months earlier, in accordance with the Israeli Ministry of Health guidelines.

Women with multiple gestations and a prior COVID-19 infection confirmed by a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test were excluded [Figure 1].

Enrolled women in both groups were recruited after vaccination via antepartum clinics and social media. Participants in both groups were contacted 2–4 weeks after delivery and were asked to complete a digital questionnaire including demographic characteristics, medical and obstetrical history, prior COVID-19 infection and vaccination record, and current pregnancy obstetric and neonatal outcomes and complications. Women were instructed to complete the obstetric and neonatal complications questionnaire according to their hospital discharge documentation.

Both groups of vaccinated pregnant women were compared for maternal characteristics as well as obstetric and early neonatal outcomes.

Hypertensive disorders of pregnancy, including gestational-induced hypertension and pre-eclampsia, were defined according to the practice bulletin of American College of Obstetricians and Gynecologists [13]. Gestational diabetes mellitus screening criteria were determined according to the Carpenter and Coustan values [14].

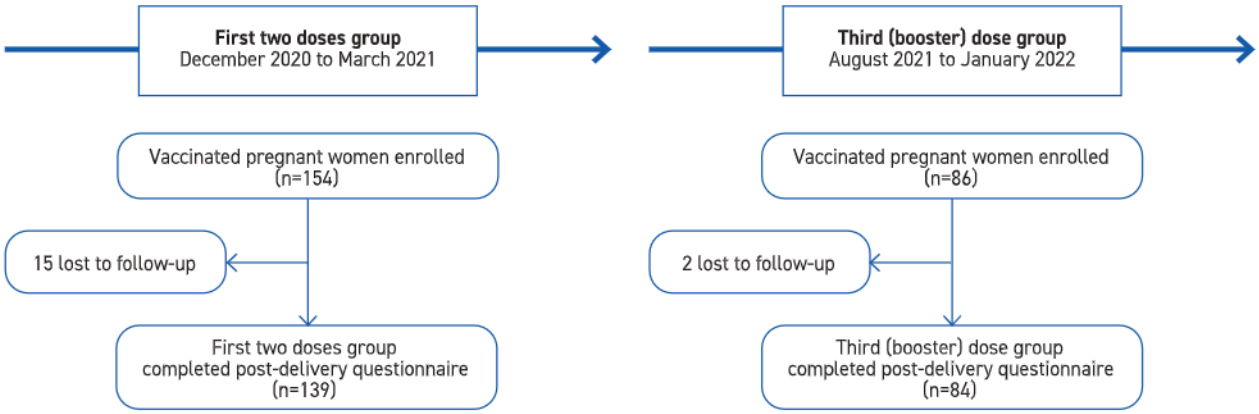
STATISTICAL ANALYSIS

Maternal characteristics between the first two doses and the third (booster) vaccination groups were compared via univariate analyses. The chi-square test and Fisher's exact test were used for categorical variables, whereas the *t*-test was used for normally distributed continuous variables. All tests were two-tailed and statistical significance was considered at P-values < 0.05.

Obstetric and neonatal outcomes were compared using a multivariant logistic regression model; covariates for adjustment were age, body mass index, presence of an autoimmune disease, lung disease, pregestational diabe-

Figure 1. Study population flow diagram

The study was conducted in two different timeframes. The first two doses group was recruited between December 2020 and March 2021 and included pregnant women vaccinated with the first two doses of the BNT162b2 (Pfizer/BioNTech) vaccine during pregnancy. The third (booster) dose group was recruited between August 2021 and January 2022 and included pregnant women vaccinated with the third dose. Inclusion criteria: vaccinated women in both groups who completed a digital questionnaire 2 to 4 weeks postpartum, women with known vaccination status and no COVID-19 infection before giving birth, and singleton births.



tes and chronic hypertension. In addition, outcomes were adjusted to the pregnancy trimester (1st / 2nd / 3rd) in which their vaccine was given. All tests were two-tailed and statistical significance was considered *P*-values < 0.05. Adjusted odds ratios (OR) are presented with 95% confidence intervals (95%CI). Statistical analysis was performed using R Statistical Software, version 4.02 (R Foundation for Statistical Computing, Vienna, Austria).

ETHICS APPROVAL

The study was approved by the Sheba Medical Center institutional review board (8008-20). All participants involved in the study provided written informed consent.

RESULTS

The study cohort included 240 pregnant women vaccinated during pregnancy during two different time frames. The study population flow is presented in Figure 1. The first timeframe included 154 pregnant women vaccinated only with the first two doses during pregnancy. The second timeframe included 86 pregnant women vaccinated with the third (booster) dose during pregnancy. Seventeen deliveries (15 in the first two doses group and 2 in the third dose group) were lost to follow-up in both groups and therefore excluded. The final study population included 223 pregnant women who were vaccinated during pregnancy: 139 pregnant women who received only the first two doses of the vaccine and 84 women who received a third (booster) dose.

Maternal characteristics were comparable between the two groups [Table 1]. The third dose group received the vaccine earlier during their pregnancy compared to the two doses group (21^{2} vs. 31^{5} weeks, respectively, $P < 0.001$).

Obstetric adverse outcomes, including rates of hypertensive disorders of pregnancy, intrauterine growth restriction and gestational diabetes were all comparable between the groups. Similarly, no differences between the groups were found with respect to complications such as placental abruption, preterm premature rupture of membranes, preterm birth, urgent cesarean delivery, intrapartum fever, and postpartum hemorrhage (PPH) [Table 2].

Early neonatal outcomes including low birth weight, APGAR < 7 at 5 minutes postpartum, neonatal transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration syndrome, intraventricular hemorrhage, the need for mechanical ventilation, and neonatal intensive care unit hospitalization were comparable between the groups [Table 2].

A multivariable regression analysis of adverse obstetric and neonatal outcomes was performed [Table 3]. The multivariable regression analysis demonstrated no increased risk of adverse obstetrics and neonatal outcome among the third dose group except from a significantly lower rate of urgent cesarean delivery among the third dose group compared to the two doses group (OR 0.21, 95%CI 0.048–0.926, $P = 0.039$).

Table 1. Maternal characteristics of pregnant women who received the first two doses compared to the third (booster) dose of the BNT162b2 vaccine

Characteristic	First two doses vaccination (n=139)	Third dose vaccination (n=84)	*P*-value
Age in years (IQR)	32.00 (22.00–42.00)	33.00 (25.00–43.00)	0.082
Body mass index, kg/m² (IQR)	23.44 (14.71–49.12)	22.42 (16.90–36.72)	0.421
Autoimmune disease	14 (10.1%)	15 (17.9%)	0.104
Lung disease	9 (6.5%)	3 (3.6%)	0.542
Pregestational diabetes	1 (0.7%)	0 (0%)	1
Chronic hypertension	0 (0%)	2 (2.4%)	0.141
Gestational age at vaccine administration, in weeks (IQR)	31^{5} (22.14–39.57)	21^{2} (7.14–36.00)	< 0.001
Vaccination during 1st trimester	0	14 (16.7%)	
Vaccination during 2nd trimester	18 (12.9%)	47 (56.0%)	
Vaccination during 3rd trimester	121 (87.1%)	23 (27.4%)	

Data are presented as median (interquartile range) or n (%)

Table 2. Adverse obstetric and neonatal outcomes after the BNT162b2 vaccine in pregnant women who received the first two doses compared to the third (booster) dose

Adverse obstetric outcome	First two doses vaccination (n=139)	Third dose vaccination (n=84)	*P*-value
Obstetric outcomes			
Hypertensive disorders of pregnancy	3 (2.2%)	4 (4.8%)	0.43
IUGR	9 (6.5%)	4 (4.8%)	0.771
Gestational diabetes	17 (12.2%)	12 (14.3%)	0.684
Placental abruption	5 (3.6%)	2 (2.4%)	0.713
PPROM	9 (6.5%)	1 (1.2%)	0.094
Preterm birth (gestational age < 37)	5 (3.6%)	4 (4.8%)	0.732
Urgent cesarean delivery	18 (12.9%)	4 (4.8%)	0.063
Intrapartum fever	5 (3.6%)	3 (3.6%)	1
Postpartum hemorrhage	7 (5%)	8 (9.5%)	0.269
Neonatal outcomes			
Birth weight in grams (IQR)	3270 (1870–4685)	3200 (1660–4390)	0.212
APGAR < 7 in 5 min	3 (2.5%)	1 (1.3%)	1
Transient tachypnea of the newborn	2 (1.4%)	0 (0%)	0.528
Respiratory distress syndrome	2 (1.4%)	3 (3.6%)	0.368
Meconium aspiration syndrome	2 (1.4%)	0 (0%)	0.528
Intraventricular hemorrhage	1 (0.7%)	0 (0%)	1
Mechanical ventilation	2 (1.4%)	1 (1.2%)	1
NICU hospitalization	5 (3.6%)	5 (6.0%)	0.508

Data are given as median (interquartile range) or n (%)
Hypertensive disorders of pregnancy include pregnancy-induced hypertension and pre-eclampsia
IUGR = intrauterine growth restriction, PPROM = preterm premature rupture of membranes, NICU = neonatal intensive care unit

DISCUSSION

In this cross-sectional study, we evaluated the effects of the third (booster) BNT162b2 vaccine given in pregnancy regarding obstetric and early neonatal outcomes. Compared to the group that received only the first two doses, no significant differences were found in all obstetric and short-term neonatal outcomes except for lower rates of urgent cesarean delivery in the third dose group.

The effects of the third (booster) vaccine should be evaluated in the context of the two additional outbreaks in Israel during the second time frame of the study: the Delta (B.1.617.2) variant in July 2021 and the Omicron (BA.1) variant in December 2021 [7]. Although different and less severe than the Alpha variant, studies have shown that both Delta and Omicron waves-associated infections of unvaccinated pregnant women were associated with higher rates of adverse pregnancy outcomes compared to earlier COVID-19 variants [15].

Contrary to the robust volume of data validating the safety and efficacy of the first two doses of the BNT162b2 vaccine in pregnancy [3-5,16,17], data regarding the obstetric and neonatal outcomes of the third BNT162b2 vaccine are still quite limited [8,9,18]. In accordance with our findings, recent retrospective studies did not demonstrate increased rates of adverse obstetric and neonatal outcomes in pregnant women vaccinated with the third (booster) vaccine compared with unvaccinated pregnant women or only two-dose vaccinated pregnant women [11,12]. However, in contrast to our findings, Dick and colleagues [11] reported higher rates of PPH among the third vaccination group.

Interestingly, we found that the risk for urgent cesarean delivery was significantly lower in the third dose vaccination group. Urgent cesarean delivery is usually performed when an immediate threat to the well-being of fetus or mother has been encountered antepartum. In contrast to our findings, Rottenstreich et al. [12] showed similar rates of urgent cesarean delivery yet higher rates of elective ce-

Table 3. Multivariable regression analysis of obstetric and neonatal outcomes

	Adjusted odds ratio (third dose vs. first two doses), 95%CI*	Adjusted *P*-value*
Late pregnancy complications		
Hypertensive disorders of pregnancy**	3.13, 0.451–21.70	0.248
IUGR	0.63, 0.127–3.10	0.569
Preterm birth	0.57, 0.086–3.84	0.567
Urgent cesarean section	0.21, 0.048–0.926	0.039
Neonatal complications		
Respiratory complications***	1.10, 0.186–6.44	0.920
NICU hospitalization	2.04, 0.383–10.90	0.403

*Adjusted to age, body mass index, presence of autoimmune disease (lung, diabetes, chronic hypertension), and vaccination trimester
**Hypertensive disorders of pregnancy included pregnancy-induced hypertension and pre-eclampsia
***Respiratory complications included respiratory distress syndrome, transient tachypnea of neonate, and meconium aspiration syndrome
95%CI = 95% confidence interval, IUGR = intrauterine growth restriction, NICU = neonatal intensive care unit

sarean delivery in 626 pregnant women vaccinated with the third dose compared with only two dose vaccinated pregnant women. This difference may be attributed to several factors: the earlier gestational stage of vaccine administration in the third dose group, the different time frame of delivery, and the relatively small sample size. Additional studies are required to clarify this issue.

Women in the third dose group were vaccinated at an earlier gestational age compared to the two doses group. This difference may be attributed to vaccine availability and relatively low compliance of pregnant women to be vaccinated with the third (booster) vaccine close to labor. The multivariant analysis was therefore adjusted to these differences.

It is important to note that participants did not report stillbirth and early neonatal death outcomes in either group. The absence of this finding may be attributed to underreporting, possibly explained by selection bias, as women with pregnancy loss were perhaps less likely to complete our digital questionnaire postpartum. Nevertheless, extensive cohort studies have not shown an increased risk for miscarriage or stillbirth in vaccinated compared to non-vaccinated pregnant women [6].

The main strengths of this study include its cross-sectional analysis of obstetric and short-term neonatal outcomes of different vaccination-level groups of pregnant women (two vs. three doses) and the study's thorough statistical analysis, eliminating known clinically relevant confounders via multivariable logistic regression model. Nevertheless, this study has several limitations. The short time frame of the third (booster) vaccine availability during the study period and low compliance led to a relatively small sample size group. Another limitation is attributed to the use of digital questionnaires, which may increase the likelihood of response bias. In addition, our study methodology did not include a comparison to a non-vaccinated pregnant women group. However, numerous studies found obstetric and neonatal outcomes of women receiving the first two doses of the BNT162b2 vaccine comparable to non-vaccinated pregnant women [3,5,6,16,19].

In summary, our study contributes to the reassuring data accumulated, suggesting that the third dose given in pregnancy is not associated with increased rates of adverse obstetric and short-term neonatal outcomes [8,9,18,20].

CONCLUSIONS

Compared to the first two doses of the BNT162b2 (Pfizer/BioNTech) vaccine given in pregnancy, the third (booster) vaccination is safe and was not associated with an increased rate of adverse obstetric and early neonatal outcomes. Further studies are required to assess long-term neonatal outcomes of infants exposed to the third (booster) BNT162b2 vaccine prenatally.

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Capsule

Aplastic anemia complicating eosinophilic fasciitis

Eosinophilic fasciitis (EF) is a disease from the scleroderma spectrum that is characterized by limb or trunk edema and erythema that evolves to collagenous thickening of the subcutaneous fascia. In the early stage of this disease, eosinophilia is a relevant laboratory finding, although not always present in active early cases and less important in later phases 1,2. Its etiology is unknown, but some possible triggers are strenuous exercises, Borrelia burgdorferi infection, and exposure to certain medications such as check point inhibitors and phenytoin. **Sakare** and colleagues searched the literature and found 10 relevant articles. In these 10 articles, 16 patients were described. The summary of the data found is reported and showed that the diagnosis of aplastic anemia (AA) in patients from 18 to 62 years of age; most were male (12/16 or 75%). AA appeared, in general, within the first year after EF diagnosis (with exception of three cases). In one case only the AA appeared prior to EF. Glucocorticoid, cyclosporine, and anti-thymocyte globulin were the most common medications. In three patients, rituximab was used, and bone marrow transplantation was initiated in four of them. While eosinophilic fasciitis is a disease with a female-to-male ratio of 1:125, the present patient series of AA in EF showed a male prevalence. Most patients were between the ages of 50 and 60. Only 5/16 were younger than 46 years old.

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Capsule

An immune atlas of developing human lungs

From birth, the airways provide protection against respiratory pathogens and inhaled toxins, but little is known about the early development of lung immune cells. Using single-cell transcriptomics, **Barnes** and colleagues characterized human embryonic and fetal immune cells in the developing lungs between 5 and 22 weeks after conception. All stages of B cell development were detected, suggesting that fetal lungs provide a local niche for B cell maturation. Myeloid cells were widespread, including near epithelial tips, and produced interleukin-1β, which induced epithelial stem cell differentiation into basal cells within fetal lung organoids. This situation provides an immune atlas of developing human lungs and suggests a role for fetal immune cells in guiding the development of the lung epithelium.

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