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Prenatal maternal COVID-19 vaccination and pregnancy outcomes

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ABSTRACT

Background: Prenatal maternal physiological changes may cause severe COVID-19 among pregnant women. The Pfizer-BioNTech COVID-19 vaccine (BNT162b2 mRNA) has been shown to be highly effective and it is recommended for individuals aged ≥16 years, including pregnant women, although the vaccine has not been tested on the latter.
Objective: To study the association between prenatal Pfizer-BioNTech COVID-19 vaccination, pregnancy course and outcomes.
Study design: A retrospective cohort study was performed, including all women who delivered between January and June 2021 at Soroka University Medical Center, the largest birth center in Israel. Excluded were women diagnosed with COVID-19 in the past, multiple gestations or unknown vaccination status. Pregnancy, delivery and newborn complications were compared between women who received 1 or 2-dose vaccines during pregnancy and unvaccinated women. Multivariable models were used to adjust for background characteristics.
Results: A total of 4,399 women participated in this study, 913 (20.8%) of which were vaccinated during pregnancy. All vaccinations occurred during second or third trimesters. As compared to the unvaccinated women, vaccinated women were older, more likely to conceive following fertility treatments, to have sufficient prenatal care, and of higher socioeconomic position. In both crude and multivariable analyses, no differences were found between the groups in pregnancy, delivery and newborn complications, including gestational age at delivery, incidence of small for gestational age and newborn respiratory complications.
Conclusions: Prenatal maternal COVID-19 vaccine has no adverse effects on pregnancy course and outcomes. These findings may help pregnant women and health care providers to make informed decision regarding vaccination.

1. Introduction

Causing more than 3.8 million deaths worldwide, COVID-19 is considered a worldwide catastrophic pandemic.[1] Numerous studies have been published on health complications of COVID-19, including studies on the physical and mental effects of COVID-19 infection during pregnancy. [2–4] The decreased lung volume with fetal growth, along with the physiological prenatal maternal immunological response suppression, [5] may cause severe COVID-19 expression among pregnant women. [6,7]

In order to defeat the pandemic, a large proportion of the population must be vaccinated. The Pfizer-BioNTech COVID-19 vaccine was approved in December 2020 by the Food and Drug Administration. [8] The vaccine, which is based on messenger-RNA technology, has been shown to be highly effective in real world setting, [9] and is recommended for use in 2-dose series separated by 21 days, for individuals aged ≥16 years. Over 2.8 billion vaccination doses, of several drug companies have been distributed worldwide, including Israel, which initiated the vaccination campaign in late December 2020. As of June 20th, >63% of the total Israeli population have been vaccinated at least once, placing Israel among the leading countries in vaccination rates per 100 people. [10] Although the vaccine has not been tested on pregnant women, medical organizations and committees, including the American College of Obstetricians and Gynecologists, [11] the Israeli Ministry of Health,[12] and the Center of Disease Control (CDC), recommend its use among pregnant women.[13] Still, vaccination is less accepted by pregnant women.[14]

The aim of the current study was to identify characteristics associated with vaccination during pregnancy, and to investigate the possible association between prenatal Pfizer-BioNTech

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COVID-19 (BNT162b2 mRNA) vaccination, and pregnancy course and outcomes.

2. Materials and methods

2.1. Study design and patients

A retrospective cohort study was conducted, including all women who delivered singletons between January and June 2021 at the Soroka University Medical Center (SUMC). SUMC which serves a population of >1 million citizens, is located in southern Israel and includes the largest birth center in the country, with >17,000 births in 2020.[15] Excluded from the study were women diagnosed with COVID-19 in the past, with multiple gestations or with unknown vaccination status and pregnancy follow-up information. Pregnancy follow-up and vaccination information was available from the "Clalit" computerized database. "Clalit" is the largest Israeli HMO, covering >70% of the Israeli population. Delivery and newborn information was available from the SUMC computerized database.

The study protocol has been approved by the SUMC IRB committee (#SOR 0085-21), and informed consent was exempt.

Pregnancy, delivery and newborn characteristics and complications were compared between women who received 1 or 2-dose vaccines during pregnancy and unvaccinated women. In a subanalysis, several characteristics were compared between women receiving 1 and 2 doses.

2.2. Variables definitions

Definitions of several variables included in the analysis are as follow: Socio economic position was a 1–10 score assigned by the Israeli Central Bureau of Statistics, based on residency; The score is based, among others, on the following characteristics of the population in the region: median age of the residents; percent of families with $\geq$4 children; mean years of education among adults; rate of residents with academic education; rate of employed residents; mean income; mean number of vehicle owned by adults.

Obesity, defined as maternal Body mass index >30; Fertility treatments included ovulation induction or in-vitro fertilization; Insufficient prenatal care was defined as $\leq$4 visits throughout pregnancy or initiation of prenatal follow-up during third trimester; Pregnancy related hypertensive disorders was defined as either mild or severe pre-eclampsia or eclampsia; Pathological presentation was a non-vertex presentation; Small for gestational age was defined as birthweight <5th percentile for gestational age and sex; Newborn respiratory complications included apnea, dyspnea, tachypnea and respiratory distress syndrome.

2.3. Statistical analysis

The comparison was performed using t-tests, Mann-Whitney U and Chi square tests. Variables that were associated with vaccination and the outcomes were suspected as confounding variables and were included in the multivariable analyses. Several multivariable regression models were used to address the possible association between vaccination status (yes/no) and the studied complications.

3. Results

A total of 6,531 women delivered during the study period, of them 4,860 (74.4%) had full data available regarding vaccination status and pregnancy follow-up, 305 (9.3%) were diagnosed with COVID-19 in their past, and 166 (3.4%) had multiple gestations (10 women had both multiple gestations and a history of COVID-19). The final study population included 4,399 women, of them 913 (20.8%) were vaccinated: 155 (17.0%) received one dose, and 758 (83.0%) received two doses. The remaining (3,486, 79.2%) were not vaccinated during or before pregnancy. All vaccinations occurred during second or third trimesters.

The comparison of background and pregnancy outcomes is presented in Table 1. As compared to the unvaccinated women, vaccinated women were older, more likely to conceive following fertility treatments, to have sufficient prenatal care and to be of higher socioeconomic position. Incidence rates of most complications were comparable between the groups. The mean time interval between first vaccination and delivery was 7.5 weeks (±4.1), the median was 7 weeks and the range was <1–21 weeks. The mean time interval between second vaccination and delivery was 5.4 weeks (±3.6), the median was 5 weeks and the range was <1–18 weeks.

Table 2 presents a comparison of main pregnancy, delivery and newborn characteristics between women who received one and two doses of the vaccination. Women who received the 2-dose vaccination delivered at slightly higher gestational age and birthweight. No differences were found between the groups in adverse outcomes incidence, however the possibility of insufficient power cannot be ruled out (Power of 18% and 20.5% to detect differences in the incidence of pregnancy related hypertensive disorders and cesarean delivery rates, respectively).

Results of the multivariable analysis are presented in Table 3. In all multivariable analyses, which adjusted for maternal age, fertility treatments and socioeconomic score, no associations were found between vaccination status and pregnancy, delivery and newborn characteristics and complications, besides lower risk for meconium stained amniotic fluid and non-reassuring fetal monitoring among the vaccinated group.

4. Discussion

In this retrospective cohort, prenatal Pfizer-BioNTech COVID-19 (BNT162b2 mRNA) vaccination was not associated with adverse immediate pregnancy outcomes or newborn complications.

While it seems the 2 dose vaccination as compared to the single dose, is associated with longer gestation and therefore increased birthweight, this finding may suggest that women received only the one dose and delivered earlier, before receiving the second one.

The BioNTech Pfizer vaccine used in Israel, is an RNA-messenger vaccine, which results in expression of vaccine-antigens that can mimic viral-antigen structure. RNA does not integrate into the genome, it is only transiently expressed, after which it is eliminated from the body, and therefore it is considered safe. [16] In both clinical trials and in real life setting, the vaccine has shown >85% reduction in the risk of symptomatic COVID-19 and its transmission. [9,17] Although not tested on pregnant women, animal studies have tested the Pfizer-BioNTech COVID-19 vaccine during pregnancy, and found no safety concerns. Additionally, no adverse effects of vaccination were reported among women who have participated in the clinical trials of the early phases of vaccination approval and became pregnant.[13] Besides the protective effect of the vaccine among the mothers, studies have suggested maternal vaccination may induce offspring immunity against COVID-19.[18,19]

In this study we were able to identify women less likely to be vaccinated, in which targeted intervention may increase vaccination compliance. While vaccination rates in the general adult population in Israel is >60%, our results show much lower vaccination rates among pregnant women. This may be due to the concern

Table 1
Comparison of background and pregnancy outcomes by vaccination status.

	Vaccinated n = 913(20.8%)	Unvaccinated n = 3,486(79.2%)	Odds ratio; 95 %CI
Maternal background characteristics			
Maternal age (mean ± SD)	30.6 ± 5.3	28.2 ± 5.7	p < 0.001
Socioeconomic score (mean ± SD)	4.51 ± 2.3	2.95 ± 2.2	p < 0.001
Obesity	152 (16.6)	549 (15.7)	1.07; 0.88–1.30
Pregnancy following fertility treatments	63 (6.9)	80 (2.3)	3.16; 2.25–4.43
Pregnancy characteristics			
Insufficient prenatal care	30 (3.3)	539 (15.5)	0.19; 0.13–0.27
Gestational diabetes mellitus	63 (6.9)	187 (5.4)	1.31; 0.97–1.76
Pregnancy complications diagnosed in late pregnancy			
Pregnancy related hypertensive disorders	50 (5.5)	165 (4.7)	1.17; 0.84–1.61
Oligohydramnios	25 (2.7)	111 (3.2)	0.86;0.55–1.33
Polyhydramnios	8 (0.9)	22 (0.6)	1.39; 0.62–3.14
Pathological presentation	36 (3.9)	132 (3.8)	1.04; 0.72–1.52
Meconium stained amniotic fluid	28 (3.1)	164 (4.7)	0.64; 0.43–0.96
Delivery and post-partum characteristics			
Gestational age at delivery (mean ± SD)	38.9 ± 1.4	39.0 ± 1.9	p = 0.13
Apgar < 7 at 5 min	2 (0.4)	30 (1.1)	0.33; 0.08–1.40
Non reassuring fetal monitoring	42 (4.6)	243 (7.0)	0.64; 0.44–0.90
Cesarean delivery	182 (19.9)	601 (17.2)	1.19; 0.99–1.44
Vacuum delivery	28 (3.1)	134 (3.8)	0.79; 0.52–1.19
Placental abruption	3 (0.3)	11(0.3)	1.04; 0.29–3.74
Postpartum hemorrhage	10 (1.1)	30 (0.9)	1.28; 0.62–2.62
Maternal postpartum fever	2 (0.2)	12 (0.3)	0.64; 0.14–2.85
Length of maternal hospitalization, days (median, range)			
Following cesarean delivery	2 (0–10)	2 (0–17)	p = 0.42
Following vaginal delivery	1 (0–7)	2 (0–10)	p = 0.21
Newborn characteristics			
Birthweight, gr. (mean ± SD)	3,224 ± 472	3,227 ± 465	p = 0.87
Small for gestational age	26 (2.8)	131 (3.8)	0.75; 0.49–1.15
Newborn respiratory complications	14 (1.5)	62 (1.8)	0.86; 0.48–1.54
Newborn fever	2 (0.2)	6 (0.2)	1.27; 0.26–6.31
Length of newborn hospitalization, days (median, range)			
Following cesarean delivery	3 (0–10)	3 (0–21)	p = 0.86
Following vaginal delivery	2 (1–7)	2 (0–26)	p = 0.46

Table 2
Main pregnancy, delivery and newborn characteristics by number of vaccination doses received.

	One dose n = 155 (17.0%)	Two doses n = 758 (83.0%)	Odds ratio; two vs. one dose; 95 %CI	Odds ratio; two dose vs. none; 95 %CI	Odds ratio; one dose vs. none; 95 %CI
Gestational age at delivery, Weeks (mean ± SD)	38.57 ± 1.48	39.0 ± 1.41	p < 0.001	p = 0.002	p = 0.91
Pregnancy related hypertensive disorders	12 (7.7)	38 (5.0)	1.54; 0.79–3.02	1.69; 0.92–3.11	1.07; 0.74–1.53
Cesarean delivery	35 (22.6)	147 (19.2)	1.16; 0.77–1.75	1.40; 0.95–2.06	1.14; 0.93–1.39
Birthweight, gr. (mean ± SD)	3,122 ± 484	3,255 ± 465	p = 0.004	p = 0.01	p = 0.24
Small for gestational age	7 (4.5)	19 (2.5)	1.82; 0.74–4.35	1.21; 0.56–2.64	0.66; 0.40–1.07
Newborn respiratory complications	3 (1.9)	11 (1.5)	1.33; 0.37–4.83		

regarding the safety of the vaccine during pregnancy, [14,20] and since clinical trials of the vaccine excluded pregnant women, it's safety during pregnancy was not addressed. All women in the current study were vaccinated during third trimester. It is possible that due to these concerns, women at late stages of pregnancy, chose to postpone the vaccination till they deliver.

The main strength of this study is the large population included, and the setting which allowed access to pregnancy follow-up, delivery and newborn information. Our findings support a recently published research by the CDC,[21] which was the first study published on this issue. The CDC study too, reported no increased risk for adverse outcomes among vaccinated women.

COVID-19 vaccination, as well as all health costs, are covered by the Israeli national universal health insurance to all Israeli citizens, therefore the study is based on a representative sample.

Since randomized clinical trials on the COVID-19 vaccination exclude pregnant women, a retrospective cohort to test the vaccine is second best research method and is required.

5. Limitations

Several limitations of the study include the insufficient power to test differences between women who received one versus two doses. In this study, all women who received at least one dose were considered as "Exposed", regardless of the time interval between the vaccination and pregnancy termination (which ranged between <1–21 weeks in this study). It is possible women should be considered as "Exposed" only several days after vaccination. However there is no clear common definition for when the vaccine is fully active among pregnant women, as well as a clear common

Table 3
Multivariable models for the association between vaccination and pregnancy, delivery and newborn characteristics and complications.

Outcomes	Adjusted Odds ratio* (vaccinated versus unvaccinated); 95 %CI
Pregnancy complications diagnosed in late pregnancy	
Pregnancy related hypertensive disorders	1.13; 0.78–1.62
Oligohydramnios	0.84; 0.52–1.40
Polyhydramnios	0.77; 0.29–2.03
Pathological presentation	0.96; 0.63–1.48
Meconium stained amniotic fluid	0.52; 0.32–0.83
Delivery and post-partum characteristics	
Gestational age at delivery	β = −0.07; (−0.26–0.11)
Non reassuring fetal monitoring	0.70; 0.48–1.01
Cesarean delivery	0.93; 0.75–1.16
Vacuum delivery	0.99; 0.63–1.57
Postpartum hemorrhage	1.46; 0.63–3.38
Maternal postpartum fever	0.73; 0.15–3.51
Newborn characteristics	
Birthweight, gr. (mean ± SD)	β = −9.14; (−55–37.5)
Small for gestational age	0.79; 0.48–1.31
Newborn postpartum fever	1.45; 0.26–8.11
Newborn respiratory complications	0.88; 0.44–1.79

*All models adjusted for maternal age, fertility treatments and socioeconomic score

definition of a precise critical window of exposure for each studied outcomes. While this may be a limitation of the study, it may have caused a beta-error of the findings. However, since most findings were null, this underestimation would have no effect on the conclusions.

Since all women in our study were vaccinated during third trimester of pregnancy the effects of vaccination during earlier stages of pregnancy could not been studied, thus our conclusions are restricted to vaccination in the third trimester of pregnancy. Lastly, due to the setting and timing, only immediate pregnancy outcomes were addressed.

Although larger studies are required to address long term and rare outcomes possibly associated with COVID-19 vaccination, as well as the effect of vaccination at earlier stages of pregnancy, the current findings support the safety of the BioNTech Pfizer vaccine regarding pregnancy and delivery complications. Current findings may be relevant for future use and safety evaluation of the RNA-messenger vaccine technology, and may help pregnant women and health care providers to make informed decision regarding vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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