Maternal and perinatal outcomes of COVID-19 vaccination during pregnancy

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Abstract

Objective: To investigate maternal adverse effects and perinatal and neonatal outcomes of women receiving coronavirus disease-2019 (COVID-19) vaccination during pregnancy.

Material and Methods: Seven hundred and sixty pregnant women who were followed up in obstetrics outpatients were included in this prospective cohort study. COVID-19 vaccination and infection histories of the patients were recorded. Demographic data, including age, parity, and presence of systemic disease and adverse events following COVID-19 vaccination were recorded. Vaccinated pregnant women were compared with unvaccinated women in terms of adverse perinatal and neonatal outcomes.

Results: Among the 760 pregnant women who met study criteria, the data of 425 pregnant women were analyzed. Among these, 55 (13%) were unvaccinated, 134 (31%) were vaccinated before pregnancy, and 236 (56%) pregnant women were vaccinated during pregnancy. Of those who were vaccinated, 307 patients (83%) received BioNTech, 52 patients (14%) received CoronaVac, and 11 patients (3%) received both CoronaVac and BioNTech. The local and systemic adverse effect profiles of patients who received COVID-19 vaccination either before or during pregnancy were similar (p=0.159), and the most common adverse effect was injection site pain. COVID-19 vaccination during pregnancy did not increase the ratio of abortion (<14 wk), stillbirth (>24 wk), preeclampsia, gestational diabetes mellitus, fetal growth restriction, second-trimester soft marker incidence, time of delivery, birth weight, preterm birth (<37 wk) or admission to the neonatal intensive care unit compared to the women who were not vaccinated during pregnacy.

Conclusion: COVID-19 vaccination during pregnancy did not increase maternal local and systemic adverse effects or poor perinatal and neonatal outcomes. Therefore, regarding the increased risk of morbidity and mortality related to COVID-19 in pregnant women, the authors propose that COVID-19 vaccination should be offered to all pregnant women. (J Turk Ger Gynecol Assoc 2023; 24: 120-4)

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Introduction

Coronavirus disease-2019 (COVID-19) remains a global public health issue, more than two years after COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11th March 2020. Pregnant women are considered a high-risk group for serious complications if the develop COVID-19. Studies have shown that pregnancies with COVID-19 are more likely to need hospitalization, intensive care unit admission, and invasive ventilation than non-pregnant patients (1). Furthermore, pregnant women with COVID-19 are reported to experience a high ratio of perinatal complications, such as preeclampsia, preterm birth, abortion, and stillbirth (2,3). Despite the increased risk, pregnant women were not included in the initial vaccination schedule (4). Up to the last quarter of 2021, the WHO recommended that pregnant women be vaccinated if they work in departments at risk of COVID-19 or have a serious chronic disease. Subsequently, the WHO recommended vaccinating pregnant women due to the serious effects of COVID-19 in pregnancy and in the light of more

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complete knowledge about vaccine safety in November 2021 (5). However, pregnant women may exhibit great hesitation about vaccination despite the updated recommendations based on both the COVID-19 infection and vaccines. At the time of writing, when there are efforts to normalise daily life, COVID-19 vaccine programs should continue to control the number of COVID-19 cases but also avoid associated morbidity and mortality in people with high risk, such as pregnant women. Therefore COVID-19 vaccination studies in pregnant women still have significant value. Thus, the aim of this study was to investigate maternal adverse effects and perinatal and neonatal outcomes associated with COVID-19 vaccination during pregnancy.

Material and Methods

The data for this prospective cohort study was collected at a University Medical Faculty, Obstetrics and Gynaecology Clinic between January 2022 and April 2022. A total of 760 pregnant women were seen in the outpatient clinic during the study data collection period. Of these, 22 multiple pregnancies, 55 pregnant women who were lost to follow-up, eight pregnant women with a history of chromosomal anomalies (four patients) or recurrent abortions (four patients), and 250 pregnant women who did not want to share their information were excluded from the study. The data of the remaining 425 pregnant women were included in the analysis. Written informed consent was signed by all participants. The study was approved by the Ankara University Ethical Committee (2021/472, date 31.12.2021). All pregnant women who agreed to participate in the study were questioned about their vaccination status and history of COVID-19 infection, regardless of their gestational wk. At the same time, the information of pregnant women who had the COVID-19 vaccination or got COVID-19 infection during the pregnancy was updated. Vaccination and infection status was confirmed via the e-NABIZ system, which is the patient registration database of the Turkish Health Ministry. The types and doses of COVID-19 vaccines were recorded. Patients who received any COVID-19 vaccine during pregnancy were divided into three groups depending on the stage of pregnancy at the time of vaccination: first trimester (<14 wk); second trimester (between ≥14 and <28 wk); and third trimester (≥28 wk). In addition, the participants were evaluated in three groups based on their medical history of COVID-19: those who have never been exposed to COVID-19 infection; those who had COVID-19 infection before pregnancy; and those who had COVID-19 infection during pregnancy.

Demographic data, including age, parity, and pre-existing systemic diseases and adverse effects associated with vaccination were documented. In addition, patients who did or did not receive vaccination during pregnancy were compared in terms of adverse pregnancy outcomes [abortion <14 wk, stillbirth >24 wk, preeclampsia, and gestational diabetes mellitus (GDM)], and neonatal outcomes [preterm birth <37 wk, congenital anomaly, fetal growth restriction, admission to neonatal intensive care unit (NICU) and neonatal death]. The pregnancy and neonatal outcomes of the COVID-19 infection history in pregnancy were also recorded.

Statistical analysis

IBM SPSS, version 26, was used for all statistical analyses (IBM Inc., Armonk, NY, USA). For assessment of normal distribution of data sets, the Kolmogorov-Smirnov test and histograms were used. Mean ± standard deviation was used to summarise normally distributed continuous variables, while the median (minimum-maximum) was used for non-normally distributed values. Categorical variables are given as n (%). Comparisons between the groups were evaluated using the Kruskal-Wallis H and Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for the categorical variables. A $p<0.05$ was considered to indicate statistical significance, and 95% confidence intervals were computed.

Results

Of the 425 participants, 55 (13%) were unvaccinated, 134 (31%) were vaccinated before pregnancy and 236 (56%) were vaccinated during pregnancy. In the latter group, 102 patients were vaccinated in the first trimester, 109 patients in the second trimester, and 24 patients in the third trimester. Demographic data of pregnant women, including age, gravidity, and accompanying comorbidities are given in Table 1.

Two types of vaccines, CoronaVac and BioNTech, were administered to a total of 370 pregnant women. Of those, 307 patients (83%) received BioNTech, 52 patients (14%) received CoronaVac, and 11 patients (3%) received both CoronaVac and BioNTech. Local and systemic adverse effects of pregnant women with a history of vaccination before or during pregnancy were recorded (Table 2). The most common adverse effect was injection-site pain. There was a statistically significant difference between those who received BioNTech and CoronaVac in terms of adverse effects ($p<0.001$). More adverse effects were observed in the group receiving BioNTech but there was no statistically significant difference between the group vaccinated before pregnancy and the group vaccinated during pregnancy in terms of adverse effects after the vaccination ($p=0.159$).

Total number of pregnancies resulting in a live birth was 395 (93%). The group vaccinated during pregnancy was compared to the group not vaccinated during pregnancy in terms of abortion (<14 wk), stillbirth (>24 wk), preeclampsia, GDM,

Table 1. Demographics variables of patients

	Unvaccinated	Vaccination before pregnancy	Vaccination during pregnancy		
			The first trimester	The second trimester	The third trimester
Total (n)	55	134	102	109	25
Maternal age (years)†	27.5±4.7	29.4±6.0	29.7±5.2	29.1±5.6	30.2±4.3
Nulliparity (n)	30 (54%)	54 (40%)	27 (26%)	27 (24%)	7 (28%)
Maternal comorbidity (n)	15 (27%)	27 (20%)	27 (26%)	28 (25%)	4 (16%)
The types of COVID-19 vaccines (n)	Pfizer-BioNTech	109 (81.3%)	90 (88.2%)	95 (87.2%)	24 (96%)
	CoronaVac	25 (18.7%)	12 (11.8%)	14 (12.8%)	1 (4%)
Vaccination time during pregnancy‡			4 (1-13)	21 (14-27)	31 (28-37)

†Mean ± standard deviation, y: years, ‡median (minimum-maximum) weeks of gestation

Table 2. Local and systemic reactions of COVID-19 vaccines

	Vaccination during pregnancy (n=236)	Vaccination before pregnancy (n=134)
No side effect	84 (36%)	58 (43%)
Injection-site pain	109 (46%)	63 (47%)
Fatigue	35 (15%)	26 (19%)
Headache	27 (11%)	14 (10%)
Myalgia	19 (8%)	14 (10%)
Injection-site swelling	14 (6%)	1 (1%)
Fever (>38 °C) or felt feverish	10 (4%)	16 (12%)
Joint pain	7 (3%)	3 (2%)
Nausea	6 (3%)	1 (1%)
Injection-site redness	5 (2%)	-
Vomiting	5 (2%)	1 (1%)
Chills	4 (2%)	1 (1%)
Diarrhea	2 (1%)	3 (2%)
Injection-site itching	1 (1%)	1 (1%)

COVID-19: Coronavirus disease-2019

fetal growth restriction, and presence of second-trimester soft markers. There was no statistically significant difference between the groups, except for abortion rates. The abortion rate in the group who did not receive the vaccine during pregnancy (20/189, 10%) was significantly higher than the group vaccinated during pregnancy (2/236, 1%), (p<0.001). The abortion rate was 3.6% (2/55) in the unvaccinated group and was 13.4% (18/134) in the group vaccinated before pregnancy. In addition, time of delivery, birth weight, preterm birth (<37 wk) and admission to the NICU did not statistically differ between the groups (Table 3). There was no neonatal mortality throughout the study.

Table 3. Pregnancy and neonatal outcomes in the pregnant women that received and did not receive the vaccine during pregnancy

	COVID-19 vaccination during pregnancy		
	Yes (n=236)	No (n=189)	p
Maternal age (y)†	29.5±5.0	28.9±5.7	0.594
Gestational age at delivery (wk)†	38.6±1.7	38.6±1.1	0.813
Birthweight (g)†	3,212±512	3,085±442	0.272
COVID-19 infection during pregnancy	26/236 (11%)	14/189 (7%)	0.205
Abortion (<14 wk)	2/236 (1%)	20/189 (10%)	<0.001
Stillbirth (>24 wk)	0	0	-
Eclampsia or preeclampsia	5/230 (2%)	1/165 (1%)	0.587
Gestational DM	9/230 (4%)	7/165 (4%)	1.0
Preterm birth (<37 wk)	13/230 (6%)	13/165 (8%)	0.753
Fetal growth restriction	7/230 (3%)	10/165 (6%)	0.421
Second-trimester soft marker	35/230 (15%)	31/165 (19%)	0.273
NICU	23/230 (10%)	7/165 (4%)	0.185
Neonatal death	0	0	-

NICU: Neonatal intensive care unit, DM: Diabetes mellitus, wk: Weeks, y: Years, g: Gram, †values are shown as mean ± standard deviation, COVID-19: Coronavirus disease-2019

Among the study participants, one fetus was terminated at the 16th gestational week due to Down syndrome, and another fetus was terminated at the 19th gestational week due to premature rupture of membranes. Both pregnant women had been vaccinated with CoronaVac before pregnancy. In the BioNTech vaccinated group, a cystic hygroma was detected in a pregnancy vaccinated in the first trimester, chorionic villus sampling was performed and routine follow-up was continued after a normal karyotype was detected. A healthy baby was born in the 39th week. Except for these, no other major foetal structural or chromosomal anomalies were detected.

COVID-19 infection during pregnancy occurred in 40 pregnant women. Ten of them were unvaccinated during the COVID-19 infection, and two pregnant women had a COVID-19 infection within 14 days after the COVID-19 vaccination. Moreover, COVID-19 infection was detected at the time of delivery in six patients. COVID-19 infection in those were either asymptomatic or with mild symptoms. Only one unvaccinated pregnant woman was admitted to the intensive care unit for seven days due to COVID-19 infection at the 13th weeks of gestation. The patient was vaccinated with two doses of BioNTech in the second trimester and no perinatal morbidity was observed during pregnancy. In terms of COVID-19 infection, 110 (26%) patients had COVID-19 before pregnancy, while 275 (65%) patients did not have a known history of COVID-19 infection.

Discussion

In addition to personal protective measures (washing hands, wearing masks, and keeping social distance) to prevent the spread of COVID-19 infection, the most powerful weapon has been vaccination, as in previous pandemics (6). Vaccination not only reduces the risk of having COVID-19 infection but also provides a milder course of symptoms in case of infection. Symptomatic COVID-19 infection during pregnancy increases the risk of maternal morbidity and mortality (7). Therefore, vaccination should not be avoided due to pregnancy. In our country, COVID-19 vaccination was begun in January 2021. Until November 2021, pregnant women could be vaccinated at their own discretion. Pregnant women were generally advised to get vaccinated after the first trimester, although there was scarce evidence. Since November 2021, vaccination has been recommended for all pregnant women, regardless of the gestational week (5).

In a recent study comparing the adverse effects of mRNA vaccines between pregnant and non-pregnant women, injection-site pain was more common in the pregnant women, while other adverse effects were more common in the non-pregnant group, but on the whole reactogenicityin these two groups was similar (8). Gray et al. (9) and Kachikis et al. (10) published similar results. In the present study, patients were vaccinated with an mRNA vaccine (BioNTech) or an inactivated vaccine (CoronaVac). Headache, injection site swelling and redness, joint pain, nausea, vomiting, and chills were more common in the group vaccinated during pregnancy while injection site pain, fatigue, myalgia, fever (>38 °C) or feeling feverish and diarrhea were more common in the group vaccinated before pregnancy. The proportion of patients without adverse effects tended to be higher in the group vaccinated before pregnancy than those vaccinated during pregnancy (43-36%, respectively; p=0.159). This difference might be attributed to the shorter time interval after vaccination in women vaccinated during pregnancy.

In a study, 140 pregnant women who received at least one dose of vaccine during pregnancy (85.7% of patients were vaccinated in the second trimester and 14.3% of patients were vaccinated in the third trimester) and 1188 unvaccinated pregnant women were compared in terms of poor pregnancy outcomes (stillbirth, fetal abnormalities, small gestational age, and admission to the NICU), and results were similar between the groups (11). In the present study, pregnant women who were vaccinated during pregnancy and who did not receive the vaccine during pregnancy were compared in terms of poor pregnancy outcomes and there was no significant difference between the groups, except for abortion rates. It is possible that pregnant women at high risk of abortion or with symptoms may have avoided the vaccination during pregnancy. In a study, Kharbanda et al. (12) examined 13160 abortions, and they found that the COVID-19 vaccine during pregnancy did not increase the risk of abortion. Furthermore, in a recently published meta-analysis of recent studies, it was demonstrated that COVID-19 vaccination during pregnancy did not increase the risk of adverse perinatal and neonatal outcomes (11,13-18).

Study Limitations

Our study had some strengths. The first was that it was a prospective study and variables such as COVID-19 vaccination and COVID-19 infection were recorded throughout the pregnancy period, since these patients were followed up and delivered in our hospital. Second, COVID-19 vaccination rates in pregnancy were high, especially in the first trimester. However, there were also some limitations. The number of patients in the study is not enough to compare perinatal outcomes. Parallel to the high rates of COVID-19 vaccination of at least one dose (93%) in our country (19), the patients in our study had a high rate of COVID-19 vaccination (87%). Therefore, since our unvaccinated pregnant rate (13%) was low, we formed two groups of those who received the COVID-19 vaccination during pregnancy and the other pregnant women, and we made all comparisons between these groups. Since BioNTech was preferred more frequently, the number of pregnant women who underwent CoronaVac was low. Again, there was no significant difference between the vaccine types in terms of maternal and neonatal adverse outcomes. We did not administer the vaccines, the patients who were vaccinated before pregnancy were not evaluated in the prospective study, and the fact that these patients may not remember the side effects of the vaccine is a limitation. Finally, COVID-19 infection screening might have resulted in low COVID-19 infection rates in our study group, since it was only symptom-based and based on personal attendance at a screening center.

Conclusion

In conclusion, pregnant women who received COVID-19 vaccination during pregnancy did not have more adverse local and systemic effects compared to the non-vaccinated women. Moreover, poor perinatal and neonatal outcomes were similar in pregnant women who received or did not receive COVID-19 vaccination during pregnancy. We propose, in light of these results and in parallel with the current literature, that COVID-19 vaccination should be offered to all pregnant women. However, long-term maternal and perinatal outcomes of vaccines containing mRNA are not known yet.

Ethics Committee Approval: *The study was approved by the Ankara University Ethical Committee (2021/472, date 31.12.2021).*

Informed Consent: *Written informed consent was signed by all participants.*

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