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Original Research

Obstetric Outcomes during COVID-19 Pandemic: Vaccination and Infection in Pregnancy

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Abstract

Background: Coronavirus disease 2019 (COVID-19) infection is associated with increased perinatal morbidity and mortality. Despite this, vaccination hesitancy among pregnant women remains to be a huge problem. In this study we aimed to evaluate COVID-19 vaccination safety and uptake in pregnancy, and to evaluate adverse perinatal outcomes associated with COVID-19 in pregnancy, compared with non-infected pregnant women. **Methods**: This is a retrospective single-institution cohort study of women who gave birth in 2021. The primary outcomes of the study were the safety of COVID-19 vaccination during pregnancy, and the comparison of perinatal outcomes in COVID-19 infected women during pregnancy group *vs* non-infected. The secondary outcomes included vaccine uptake rate, trimester evaluation of vaccination safety, and side effects. **Results**: Among 3620 deliveries, 1943 individuals who were vaccine eligible before delivery were included in the vaccine safety and uptake analysis. Out of 1943 pregnant women, 212 (10.9%) women received at least one dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine during pregnancy. 189 (89.2%) of them received BNT162b2 (Pfizer/BioNTech) and 23 (10.8%) CoronaVac (Sinovac). Following propensity score matching, no significant increase in emergency cesarean section (C-section) rates, intrapartum complications, stillbirth, congenital anomalies, maternal or neonatal intensive care unit (NICU) admissions were found in COVID-19 vaccinated group compared to the non-vaccinated ($p > 0.05$, for all). 436 women with a history of COVID-19 polymerase chain reaction (PCR) positivity during pregnancy were compared with 2972 women who tested negative. No overall significant adverse effects were identified due to COVID-19 infection during pregnancy. Perinatal outcomes were similar in both groups ($p > 0.05$, for all). In the subgroup analysis of 212 pregnant women vaccinated during pregnancy, NICU admission was lowest in the third trimester group ($p < 0.001$). Antenatal vaccine uptake was higher among women with pregestational diabetes, hypothyroidism and autoimmune diseases compared to the overall vaccination rate (23%, 14%, 20.8% and 10.9% respectively). **Conclusions**: In this study, COVID-19 vaccination in pregnancy was not associated with significant adverse perinatal outcomes. Overall, COVID-19 infection was not associated with increased adverse perinatal outcomes. Our results should be confirmed in a bigger cohort in order to draw more definite conclusions.

Keywords: COVID-19; inactivated vaccine; mRNA vaccines; pregnancy outcome; safety; SARS-CoV-2

1. Introduction

At the beginning of coronavirus disease 2019 (COVID-19) pandemic it was unclear whether pregnant women were more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent studies show that COVID-19 infection is associated with increased perinatal morbidity and mortality. However, which negative perinatal outcome the infection is associated with is still controversial. In a study published in 2021, it was shown that the severe perinatal morbidity and mortality rate was more than twice as high in COVID-19 infected women [1]. Another study reported the risk of neonatal adverse outcome was 1.45 times increased, while rates of emergency cesarean section (C-section), preeclampsia, and preterm birth were found to be increased [2]. In a meta-analysis, preeclampsia rates were found to be increased 1.42 times, with neonatal intensive care unit (NICU) admissions being increased 1.86 times. No differences in maternal hemorrhage, placental abruption, or emergency C-section were noted [3]. Chmielewska *et al*. [4], found that maternal mortality and stillbirth were increased when interpreting data from low-middle income countries. However, they found no overall significant effect on other adverse perinatal outcomes in a meta-analysis in which they suggested that the increased rate of adverse outcomes might be driven by the inefficiency of the health-care system. Therefore, public health measures, including vaccination and disease management are crucial to protect both the pregnant women and their fetuses.

Although the long-term safety profile of COVID-19 vaccination regarding pregnant women is lacking, accumulated data suggest that the known risks of the infection outweigh the potential unknown risks of the vaccination [5]. Vaccination hesitancy among pregnant women

is high, which is contradictory to the recommendations of healthcare professionals about susceptible populations [6,7]. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) recommend that COVID-19 vaccines should not be withheld on the basis of pregnancy [8]. In a study including 1328 pregnant women eligible for a COVID-19 vaccine, it was shown that only 28.5% accepted vaccination during pregnancy [9]. Even in a large population-based cohort study including 97,590 individuals, vaccination in pregnancy was reported as low as 23% [10]. From a national study at the beginning of 2021, the intention of pregnant women to get vaccinated was reported to be around 37% if it was recommended during pregnancy [11].

In this study, we aimed to investigate the uptake rate and safety of COVID-19 vaccines, and to evaluate the perinatal outcomes of COVID-19 infection among pregnant women in comparison to non-infected pregnant women.

2. Material and Methods

2.1 Study Design

This was a retrospective cohort study of pregnant women who gave birth in Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Turkey, between 01/01/2021 and 12/31/2021. Data was collected from the hospital's electronic health information system. Women with unknown last menstrual period or no first trimester scanning were excluded.

Maternal age, ethnicity, parity, obstetric history, pregestational and gestational diseases, and obstetric outcomes were recorded. COVID-19 infection and vaccination status of the participants along with local and systemic side effects due to vaccination during pregnancy were obtained from the national public health management system. COVID-19 infection was confirmed with a polymerase chain reaction (PCR) test at the time of admission to labor and delivery ward or at the time of suspected infection. Vaccine types available in our country were messenger RNA (mRNA) BNT162b2 (Pfizer/BioNTech) and inactivated vaccine CoronaVac (Sinovac).

According to the national vaccination program in our country, by June 24, 2021, all pregnant women were eligible for COVID-19 vaccination of their own choice, including CoronaVac and BNT162b2. Therefore, pregnant women who gave birth after vaccine eligibility were included for statistical analysis of vaccination safety and side effects.

The safety of COVID-19 vaccination, and comparison of perinatal outcomes in COVID-19 infected and non-infected groups during pregnancy, were the primary outcomes of the study. Perinatal outcomes both to assess the safety of vaccination and for the comparison of COVID-19 infection effect included birthweight, mode of delivery, stillbirth (fetal death $>$24 weeks), intrapartum complications (fetal distress, placental abruption, preeclampsia/eclampsia/hemolysis, elevated liver enzymes and low platelet syndrome (HELLP), chorioamnionitis), fetal anomalies, Apgar scores, maternal and NICU admissions, and maternal death. Vaccine uptake criterion was accepted as having a minimum of 1 dose of COVID-19 vaccine done during pregnancy. Patients with a history of confirmed COVID infection, before or during their pregnancy, and COVID-19 vaccination receipt before pregnancy, were excluded. For vaccine safety analysis, perinatal outcomes were compared between the group of women who received a minimum of 1 dose of COVID-19 vaccine during pregnancy and the group of women who did not receive any COVID-19 vaccine during pregnancy. To evaluate the adverse perinatal outcomes due to COVID-19 infection during pregnancy, they were compared between two groups: COVID-19 infected during pregnancy *vs* non-infected.

Secondary outcomes of this study were vaccine uptake rates, trimester evaluation of the perinatal outcomes, and side-effects among the vaccinated group.

2.2 Statistical Analysis

We performed normality tests of the distribution of continuous variables via Kolmogorov-Smirnov test. For the distribution of the quantitative variables which did not fit the normal distribution, the Mann-Whitney U test was used to determine the significance of the difference between two independent groups. For categorical variables, we used Pearson Chi-square, Continuity Correction (Yates Chi-square) or Fisher's Exact test for the significance of the difference in the rates between two independent groups. Here, we made the selection according to the expected frequencies and we made evaluations for all variables separately.

For the comparison of perinatal outcomes between antenatally COVID-19 vaccinated and non-vaccinated individuals, we used propensity score matching to eliminate potential confounders. We determined potential covariates considering the factors identified in group comparison with the p-values of <0.1. The cases were matched 1:2 K-Nearest Neighbor (K-NN). The success of the matching was assessed both using variance ratio (VR) and standard mean difference (SMD). SMD value of <0.1 was taken as balance was reached. We reported effect magnitudes of vaccination on perinatal outcomes as odds ratio (OR) with 95% confidence intervals (95% CIs).

For trimester adverse effect outcome analysis, we performed One-Way Analysis of Variance (ANOVA) test for the significance of the difference between the means of three independent samples, which were normally distributed. For other variables, we applied non-parametric Kruskal Wallis H test.

We used R statistical analysis software (R Project 4.1.1, R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.

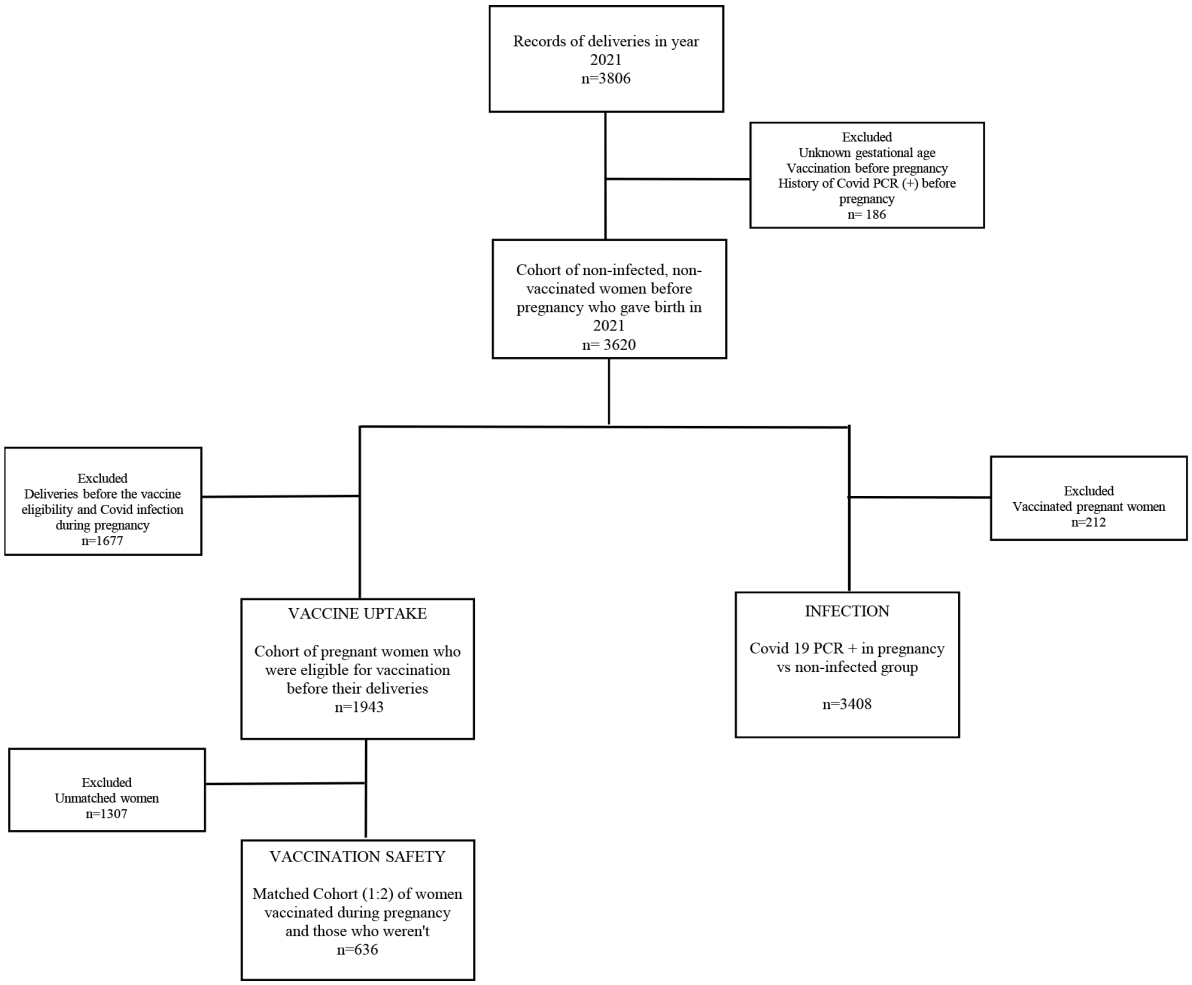

Fig. 1. Study flow diagram. COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

3. Results

A total of 3806 pregnant women were eligible for the study. The study flow diagram is provided in Fig. 1. 186 individuals were excluded due to missing data, vaccination before pregnancy, or history of COVID seropositivity before pregnancy. There were 3620 deliveries in 2021 which were included in the study, in Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology. For the vaccine safety and uptake analysis, 1943 individuals who were vaccine eligible before delivery were included.

Out of 1943 women, 212 (10.9%) received at least 1 dose of SARS-CoV-2 vaccine during pregnancy. 1731 non-vaccinated pregnant women and 212 vaccinated women were compared in terms of demographic characteristics and perinatal outcomes. The baseline characteristics of the 2 groups are given in Table 1. Among the vaccinated group, 189 pregnant women received BNT162b2 (89.2%), and 23 received CoronaVac (10.8%). The mean age of the vaccinated group was higher, compared to the unvaccinated group (29.7 *vs* 27.7, $p < 0.001$). Apart from pregestational hypertension, there was no significant difference in pregestational diseases between the two groups ($p > 0.05$). While gestational diabetes was found to be higher in the vaccinated group, there was no difference in terms of other antenatal complications ($p = 0.029$, $p > 0.05$ respectively) (Table 1).

Uptake of COVID-19 vaccination was higher among Turkish individuals compared to Syrian ethnic and other ethnic groups (13.3%, 0.6% and 2%). Among COVID-19 vaccine-eligible pregnant individuals 385 (19.8%) had a systemic disease, and 52 (13.5%) of these pregnant individuals had received COVID-19 vaccination during pregnancy. Antenatal vaccine uptake was higher among women with pregestational diabetes compared to the overall vaccination rate (23% *vs* 10.9%). The vaccination rate among 178 individuals with hypothyroidism was 14%, 14.5% among 200 individuals who were using anticoagulants, and 20.8% among individuals with an autoimmune disease. 13.1% of pregnant individuals who were smoking during pregnancy had received vaccination.

3.1 Propensity-Matched Cohort

Following 1:2 propensity score matching, standardized differences less than 0.1 were balanced, and the overlap

Table 1. Baseline characteristics of women who received at least one dose of COVID-19 vaccine during pregnancy and who did not.

	Received ≥1 dose of COVID-19 vaccine during pregnancy	Did not receive any COVID-19 vaccine	*p*-value	SMD**
	n (%)	n (%)		
n	212 (10.9)	1731 (89.1)		
Vaccine Type			<0.001	1.78
BNT162b2 (mRNA)	189 (89.2)	-	-	-
CoronaVac (inactivated)	23 (10.8)	-	-	-
Maternal Age (years) (mean)	29.7 (5.8)*	27.7 (5.7)*	<0.001	0.35
Ethnicity			<0.001	0.666
Turkish	209 (98.6)	1359 (78.5)		
Syrian	2 (0.9)	324 (18.7)		
Others	1 (0.5)	48 (2.8)		
Multiparous	166 (78.3)	1283 (74.1)	0.216	0.098
Pregestational Maternal Systemic Diseases	52 (24.5)	333 (19.2)	0.083	0.128
Hypertension	6 (2.8)	14 (0.8)	0.017	0.152
Diabetes Mellitus	6 (2.8)	20 (1.2)	0.092	0.12
Hypothyroidism	25 (11.8)	153 (8.8)	0.200	0.097
Hyperthyroidism	0 (0.0)	3 (0.2)	>0.999	0.059
Cardiac Disease	1 (0.5)	20 (1.2)	0.578	0.076
Pulmonary Disease	2 (0.9)	34 (2.0)	0.441	0.085
Renal Disease	0 (0.0)	8 (0.5)	0.672	0.096
Autoimmune Disease	5 (2.4)	19 (1.1)	0.215	0.097
Neurological Disease	2 (0.9)	23 (1.3)	0.883	0.036
Infectious Disease	11 (5.2)	63 (3.6)	0.356	0.075
Smoking during pregnancy	27 (12.7)	179 (10.3)	0.342	0.075
Antenatal anticoagulant use during pregnancy	29 (13.7)	171 (9.9)	0.110	0.118
Aspirin	8 (3.8)	35 (2.0)	0.165	0.105
LMWH[a]	4 (1.9)	36 (2.1)	>0.999	0.014
Both	17 (8.0)	100 (5.8)	0.253	0.089
Multiple Pregnancy	6 (2.8)	19 (1.1)	0.073	0.125
Antenatal Complications	55 (25.9)	372 (21.5)	0.165	0.105
Gestational Diabetes	23 (10.8)	113 (6.5)	0.029	0.154
Gestational Hypertension	2 (0.9)	32 (1.8)	0.502	0.077
Preeclampsia	10 (4.7)	44 (2.5)	0.110	0.116
Cholestasis	1 (0.5)	15 (0.9)	0.843	0.048
IUGR[b]	7 (3.3)	65 (3.8)	0.891	0.025
Preterm birth	6 (2.8)	43 (2.5)	0.943	0.022

[a] LMWH, Low molecular weight heparin.

[b] IUGR, Intrauterine growth restriction.

* SD, Standard deviation.

** SMD, Standardized mean difference.

in distributions was confirmed. 212 women who received at least one dose of COVID-19 vaccine in pregnancy were matched with 424 women who did not. There was no significant difference in mode of delivery, intrapartum complications, or NICU admissions ($p > 0.05$, for all). Despite statistically significant differences in the two groups in terms of birthweight and 5th minute Apgar score, the values were clinically insignificant ($p = 0.027$, $p = 0.013$, respectively). COVID-19 vaccination during pregnancy was not associated with a significant increase in the risk of fetal distress, (5.2% *vs* 9%, relative risk (RR) 0.54 [95% CI, 0.22 to 1.09]) preeclampsia (2.8% *vs* 1.7%, RR 1.85 [95% CI, 0.46 to 6.45]), congenital anomalies (7.1% *vs* 9.9%, RR 0.68 [95% CI, 0.43 to 1.15]) or stillbirth (1.4% *vs* 1.2%, RR 1.44 [95% CI, 0 to 9.29]) (Table 2).

Table 2. Perinatal outcomes of propensity score matched groups of women who received at least one dose of COVID-19 vaccine during pregnancy and those who did not.

	Received ≥1 dose of COVID-19 vaccine during pregnancy	Did not receive any COVID-19 vaccine	Effect magnitude (95% CI*)	*p*-value
	n (%)	n (%)		
n	212	424		
Emergency C-section[a]	60 (28.3)	125 (29.5)	0.95 (0.68–1.36)	0.773
Maternal ICU[b] admission	0 (0.0)	1 (0.2)	NE**	NE**
Birthweight (g)	3100.63 (700.51)***	3228.19 (713.62)***	–130.5 (–245.98– –15.03)	0.027
Apgar Score 5th min	9.32 (0.94)***	9.09 (1.25)***	0.24 (0.05–0.44)	0.013
Intrapartum Complications				
Fetal Distress	11 (5.2)	38 (9.0)	0.54 (0.22–1.09)	0.090
Preeclampsia	6 (2.8)	7 (1.7)	1.85 (0.46–6.45)	0.269
Placental Abruption	0 (0.0)	9 (2.1)	NE**	NE**
Chorioamnionitis	1 (0.5)	0 (0.0)	NE**	NE**
Stillbirth	3 (1.4)	5 (1.2)	1.44 (0–9.29)	0.639
Congenital Anomalies	15 (7.1)	42 (9.9)	0.68 (0.43–1.15)	0.132
NICU[c] admission	57 (26.9)	99 (23.3)	1.21 (0.87–1.76)	0.259

Covariates: Maternal age, smoking, antenatal anticoagulant use (aspirin, LMWH), maternal systemic disease (hypertension, pulmonary disease).

* CI, Confidence interval; ** NE, Not estimable; *** SD, Standard deviation.

[a] C-section, cesarean section; [b] ICU, Intensive care unit; [c] NICU, Neonatal intensive care unit.

3.2 Comparison of COVID-19 Seropositive and Negative Groups

To determine the effect of COVID-19 infection in pregnancy on perinatal outcomes, 212 vaccinated pregnant women were excluded from the 3620 pregnant women without a history of COVID-19 infection or vaccination before pregnancy. The baseline characteristics of the 3408 women were divided into two groups: COVID-19 seropositive and negative, presented in Table 3. In the COVID-19 seropositive group, 102 (23.4%) pregnant women had a pregestational chronic disease. Compared to the seronegative group, the seropositive group had significantly higher pregestational hypothyroidism (7.1% *vs* 12.2%, $p < 0.001$). The smoking rate was higher in the seronegative group ($p = 0.002$). The 2 groups were similar in terms of antenatal anticoagulant (aspirin and low molecular weight heparin (LMWH)) use, multiple pregnancy, gestational age at birth, mode of delivery, and maternal intensive care unit admission ($p > 0.05$, for all) (Table 3). Also, there was no difference in neonatal birthweight, 5th minute Apgar score, intrapartum complications (fetal distress, preeclampsia, eclampsia, and placental abruption), NICU admission, or stillbirth ($p > 0.05$, for all (Table 3)).

3.3 Trimester Analysis

In the subgroup analysis of 212 pregnant women vaccinated during pregnancy, vaccine 1st dose uptake according to trimester was determined to be 3.3% in the first trimester, 38% in the second, and 58% in the third trimester. Gestational age distribution of vaccinations is shown in Fig. 2, and shows a very low vaccination rate in the first trimester. All pregnant women in the first trimester group received BNT162b2, whereas the ratios were 84.1% in the second trimester, and 92.6% in the third trimester. There was no difference in 3 groups in terms of maternal age, ethnicity, and pregestational maternal chronic diseases ($p > 0.05$, for all). Gestational age at birth was similar in the second and third trimester groups (37.26 *vs* 38.84 weeks). NICU admission was lower in the third trimester compared to the first and second trimester vaccination groups (16.4% *vs* 50.0% and 32.9%) (Table 4).

Of the vaccinated women, 17% experienced local side effects and 13.2% systemic side effects from the vaccine. Local side effects included swelling and localized pain at the injection site and were reported to be similar between the second and third trimester groups (15.9% *vs* 16.4%). Fatigue and myalgia were the most common reported systemic side effects. Two pregnant individuals who received their first vaccine dose in third trimester described temporary uterine contractions. None of the women reported vaginal bleeding after vaccination.

4. Discussion

In this study, BNT162b2 or CoronaVac vaccination during pregnancy was not associated with statistically significant adverse perinatal outcomes. These findings support the recommendation of vaccination in pregnancy, especially, during the second and third trimesters.

In a study conducted in Canada, Fell *et al.* [10] found that vaccination during pregnancy with Pfizer BioN-

Table 3. Baseline characteristics and perinatal outcomes of women who had a COVID-19 PCR positive result during pregnancy and those who did not.

	COVID-19 PCR positivity during pregnancy	COVID-19 PCR negative	*p*-value
	n (%)	n (%)	
n	436 (12.8)	2972 (87.2)	
Maternal Age (years) (mean)	28.3 (0.27)*	27.7 (0.12)*	0.062
Ethnicity			
Turkish	395 (90.6)	2322 (78.1)	<0.001
Syrian	35 (8.0)	577 (19.4)	<0.001
Others	6 (1.4)	73 (2.5)	0.017
Multiparous	324 (74.3)	2254 (75.8)	0.487
Pregestational Maternal Chronic Diseases	102 (23.4)	507 (17.1)	0.002
Hypertension	4 (0.9)	29 (1.0)	>0.999
Diabetes Mellitus	4 (0.9)	32 (1.2)	0.685
Hypothyroidism	53 (12.2)	210 (7.1)	<0.001
Hyperthyroidism	2 (0.5)	8 (0.3)	0.678
Cardiac Disease	5 (1.1)	36 (1.2)	>0.999
Pulmonary Disease	6 (1.4)	56 (1.9)	0.496
Renal Disease	1 (0.2)	9 (0.3)	>0.999
Autoimmune Disease	6 (1.4)	12 (0.4)	0.073
Neurological Disease	2 (0.5)	27 (0.9)	0.615
Infectious Disease	19 (4.4)	89 (3.0)	0.129
Smoking during pregnancy	26 (6.0)	321 (10.8)	0.002
Antenatal anticoagulant use during pregnancy			
Aspirin	14 (3.2)	67 (2.3)	0.177
LMWH[a]	11 (2.5)	52 (1.7)	0.177
Both	28 (6.4)	142 (4.8)	0.377
Multiple Pregnancy	3 (0.7)	38 (1.3)	0.412
Gestational age at delivery (week)	38.44 (0.11)*	38.46 (0.04)*	0.954
Mode of Delivery			
Unassisted Vaginal	212 (48.6)	1610 (54.2)	0.051
Emergency C-section	101 (23.2)	734 (24.7)	0.366
Elective C-section	123 (28.2)	628 (21.1)	0.053
Maternal ICU[b] admission	3 (0.7)	8 (0.3)	0.157
Maternal Death	1 (0)	0 (0)	NE**
NICU[c] admission	88 (20.2)	547 (18.4)	0.373
Antenatal Complications	105 (24.1)	634 (21.3)	0.192
Birthweight (g)	3178.32 (29.43)*	3180.3 (11.16)*	0.485
Apgar Score 5th min	9.23 (0.07)*	9.26 (0.03)*	0.559
Congenital Anomalies	19 (4.4)	197 (6.6)	0.069
Intrapartum Complications			
Fetal Distress	34 (7.8)	256 (8.6)	0.582
Preeclampsia, Eclampsia	6 (1.4)	33 (1.1)	0.638
Placental Abruption	1 (0.2)	31 (1.0)	0.258
Chorioamnionitis	0 (0)	1 (0)	NE**
COVID-19 related C-section	0 (0)	1 (0)	NE**
Stillbirth = 1 (%)	3 (0.7)	10 (0.3)	0.48

* SD, Standard deviation; ** NE, Not estimable.

[a] LMWH, Low molecular weight heparin.

[b] ICU, Intensive care unit.

[c] NICU, Neonatal intensive care unit.

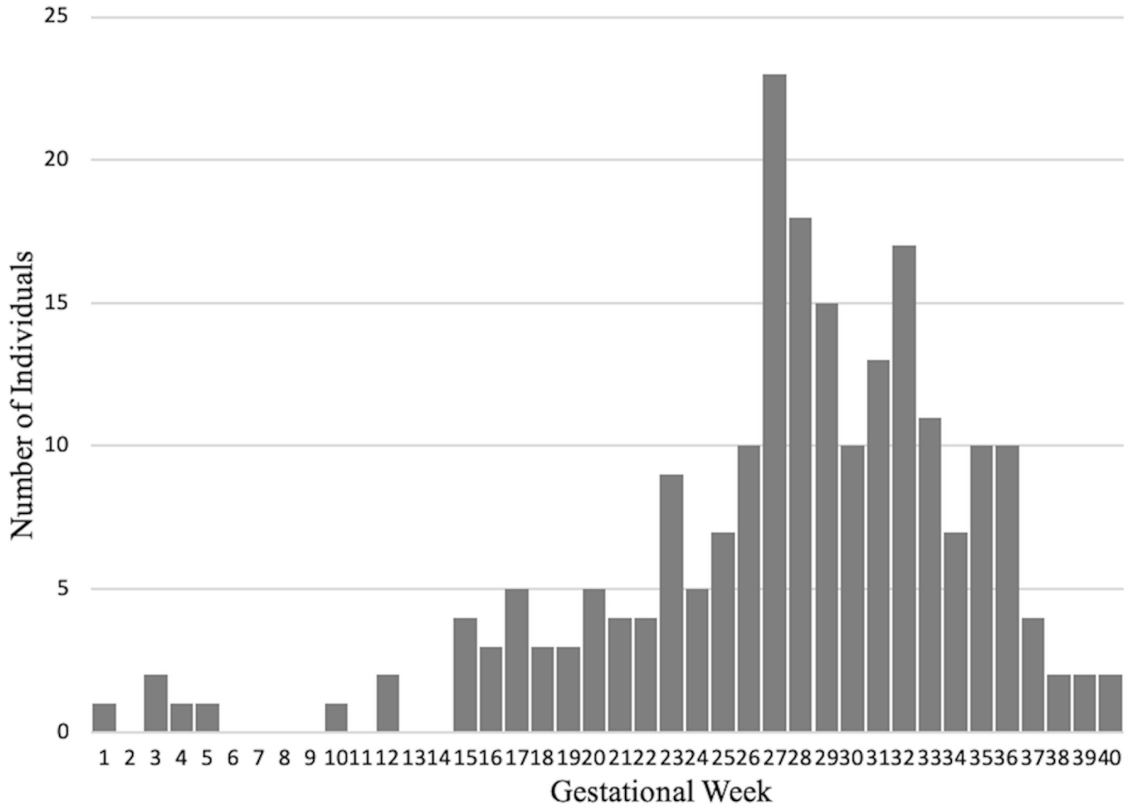

Fig. 2. Gestational age distribution at receipt of dose 1 during pregnancy.

Tech BNT162b2, Moderna mRNA-1273, or AstraZeneca AZD1222 vaccines was not associated with an increased risk of post-partum adverse outcomes, such as postpartum hemorrhage, chorioamnionitis, cesarean delivery, admission to NICU, or low 5th minute Apgar score. In a different study, Magnus *et al*. [12] reported no significant increase in pregnancy complications among the vaccinated group compared to the unvaccinated group. The vaccine of choice among the vaccinated group was BNT162b2, and the majority of vaccinations were in the second and third trimesters. The findings of a meta-analysis by Prasad *et al*. [13] concluded that there was no increase in any adverse outcome examined for the mother or the baby. They stated that there was some evidence of benefit, such as a 15% decrease in stillbirths in the vaccinated group during pregnancy compared to the unvaccinated group [13]. These cumulative data are important to increase the vaccination rates in pregnancy throughout the world since the pregnant population is at a higher risk of severe COVID-19 infection [14]. Our findings are in concordance with these studies, which found no adverse perinatal outcomes following SARS-CoV-2 vaccines during pregnancy.

There are several well-known risk factors associated with mortality among COVID-19 infected individuals. Older age, diabetes mellitus and hypertension were reported to increase the risk of mortality [15–17]. In a meta-analysis including 33 country territories, pregnant women with comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease were at increased risk for severe maternal and fetal COVID-19 related outcomes [3]. In our study, we found that pregnant individuals with comorbidities had received at least one dose of COVID-19 vaccine at a rate of 13.5%, higher than the overall vaccination rate, which was 10.9%. Pregnant women with pregestational diabetes, infectious diseases, autoimmune diseases, and who were smokers during pregnancy got vaccinated at a higher rate than the average. Whereas individuals with cardiac diseases had very lower vaccination rate in contrast to expectations.

COVID-19 vaccination campaigns have been carried out throughout the world, and in February 2022, according to United States data, it has been reported that 68% of pregnant individuals have completed their vaccine series [18]. A cross-sectional survey done in United States from August to December 2020, reported that only 41% of the pregnant participants were willing to get vaccinated for COVID-19 if they were eligible [19]. In a meta-analysis evaluating COVID-19 vaccine uptake rates and predictors of vaccination receipt, the overall COVID-19 uptake rate was found to be 27.5% [6]. The majority of the studies in this study were from high-income countries. The predictors of getting COVID-19 vaccination were reported to be older age, trust in COVID-19 vaccines, fear of COVID-19 infection during pregnancy, and pregestational diabetes [6].

Table 4. Trimester wise analysis of COVID-19 vaccine uptake and side-effects.

	1st Trimester	2nd Trimester	3rd Trimester	*p*-value
	n (%)	n (%)	n (%)	
n	8	82	122	
Vaccine Type				0.73
BNT162b2 (mRNA)	8 (100)	69 (84.1)	113 (92.6)	
CoronaVac (inactivated)	0 (0)	13 (15.9)	9 (7.4)	
Maternal Age (years) (mean)	28.9 (3.87)*	30.3 (5.58)*	29.1 (5.94)*	0.34
Ethnicity				0.91
Turkish	8 (100)	81 (98.8)	120 (98.4)	
Syrian	0 (0)	1 (1.2)	1 (0.8)	
Other	0 (0)	0 (0)	1 (0.8)	
Gestational age at vaccination 1st dose (week)	8.73 (1.58)	23.41 (0.37)	32.04 (0.26)	<0.001
Pregestational Maternal Chronic Diseases	2 (25.0)	23 (28.0)	28 (23.0)	0.63
Smoking during pregnancy	3 (37.5)	6 (7.3)	15 (12.3)	0.03
Birthweight (g)	2305.45 (1109.40)*	3028.30 (793.30)*	3200.21 (537.92)*	0.02
Gestational age at birth (week)	34.12 (7.47)	37.26 (2.99)	38.84 (1.69)	<0.001
Congenital Anomalies	1 (12.5)	7 (8.5)	4 (3.3)	0.74
Maternal ICU[a] admission	0 (0)	0 (0)	0 (0)	NE**
Maternal Death	0 (0)	0 (0)	0 (0)	NE**
NICU[b] admission	4 (50.0)	27 (32.9)	18 (16.4)	<0.001
Local Side Effects after vaccination 1st dose	3 (37.5)	13 (15.9)	20 (16.4)	0.047
Systemic side effects after vaccination 1st dose	2 (25)	11 (13.4)	15 (12.3)	0.08
Fever	1 (12.5)	0 (0)	2 (1.6)	0.04
Fatigue	1 (12.5)	7 (8.5)	6 (4.9)	0.15
Myalgia-Arthralgia	1 (12.5)	5 (6.1)	3 (2.5)	0.04
Headache	1 (12.5)	0 (0)	2 (1.6)	NE**
Vaginal Bleeding	0 (0)	0 (0)	0 (0)	NE**
Uterine Contraction	0 (0)	0 (0)	2 (1.6)	NE**

* SD, Standard deviation. ** NE, Not estimable.

[a] ICU, Intensive care unit.

[b] NICU, Neonatal intensive care unit.

A study including 623 pregnant women in Sudan found that only 2.7% of individuals were willing to receive COVID-19 vaccine during pregnancy [20]. In a meta-analysis including 17 studies in which 5 of them were from low-middle income countries, the overall vaccine acceptance rate was reported to be 49% [21]. In a global mapping study, including 519 articles, pregnant and breastfeeding individuals were reported to have the lowest vaccine acceptance and uptake rate of 54% and 7% respectively, compared to other population groups [22]. A study from our country, Turkey, found that 37% of pregnant women had an intention of receiving COVID-19 vaccine [11]. However, in our study we found a vaccine uptake rate of 10.9%.

Globally, there is a large gap between COVID-19 vaccine acceptance and uptake rates [22]. Vaccine hesitancy remains to be a huge problem. As Bhattacharya *et al.* [21] mentioned in their study, similar trends were observed in the uptake of influenza vaccines in the previous pandemic. In 2017, the most frequent barriers to pandemic influenza vaccine uptake for pregnant individuals included vaccine safety concerns, mistrust ineffectiveness of the vaccine and misconceptions about the vaccine [23]. A study from our country reported comparable reasons among pregnant women refusing to receive COVID-19 vaccines, including lack of data on the safety of the vaccine in pregnant population, possible harm to the fetus and mistrust in the efficacy of COVID-19 vaccines [11].

An understanding of the factors related to increased COVID-19 vaccine uptake in pregnant women is crucial to use appropriate communication tools. A national study pointed out that the ratio of pregnant women in the vaccine acceptance group who thought that they were informed adequately about the COVID-19 vaccine was significantly higher than in the vaccine refusal group [11]. Therefore, the main strategy to overcome vaccine hesitancy should be to inform target groups and provide necessary data regarding the safety and efficacy of COVID-19 vaccines in order to improve trust in the vaccines. Media sources and public information tools should be used effectively to increase the vaccination rates as these are the main channels where the vaccine acceptance group thought that they were informed adequately [11]. These highlight the need for per-

sistent public education campaigns, promotion of the vaccine by health institutions, and a systematic monitorization of vaccine uptake among risk groups.

In a meta-analysis which included 111 studies, enrolling 42,754 COVID-19-positive pregnant women, the risk of low-birth weight, premature delivery, preeclampsia, and stillbirth was higher in COVID-19 seropositive pregnant women compared to non-infected. The authors concluded that there was no evidence of an increased maternal mortality in pregnant women infected with COVID-19 [24]. In parallel, we found no significant increased risk of preeclampsia, premature delivery, maternal or NICU admission in the COVID-19 infected group compared to the non-infected group.

A recent study with a large sample size of vaccinated pregnant women claimed that the women vaccinated in the second trimester were more likely to have a preterm birth compared to their nonvaccinated counterparts [25]. In contrast, in our trimester analysis we found out that the pregnant individuals vaccinated in the first trimester, delivered before term and had a lower birthweight. In a mega-cohort from Liu *et al*. [26], any women smoking during the three months prior to conception and who continued smoking into the first trimester of pregnancy was associated with increased preterm birth compared to nonsmokers. Accordingly, we believe that the high smoking rates we found in the first trimester group may have potentially contributed to the increased rates of preterm birth.

In a mini-review by Chen *et al*. [5], it was mentioned that higher placental antibody transfer ratio was associated with increasing duration between maternal vaccination and delivery. They summarized that maternal vaccination starting from the early second trimester might be an optimal time for newborn immunity against SARS-CoV-2 infection, since the placental antibody transfer begins from the 17th week of pregnancy. In contrast, a study evaluating maternal and cord blood antibody levels at birth after mRNA COVID-19 vaccination during the second trimester of pregnancy demonstrated that antibody levels fade in the maternal circulation as time passes, implying that the impact of antenatal vaccination timing may influence neonatal seroprotection. They concluded that a booster dose might be beneficial for those who completed the two-dose vaccine series before conception, or in the early gestational period [27]. In our study, we found that NICU admission was lower in the group who received the 1st dose of COVID-19 vaccine in the early third trimester compared to the groups who received the vaccine in the first or second trimester. Further studies on fading maternal antibody levels and its time course might be useful in order to interpret our findings.

To our knowledge this study is the first study that includes CoronaVac inactivated vaccine in the vaccinated pregnant group, comparing perinatal outcomes in two propensity score matched groups. Although CoronaVac is the first COVID-19 vaccine proposed in our country, by the time of eligibility for pregnant women, BNT162b2 and CoronaVac were the two COVID-19 vaccines available. We found out that the majority (89.2%) of women received at least one dose of BNT162b2 during their pregnancy. We believe that the scarcity of transparently published data on CoronaVac may have led to this result [28].

Data in our study are from a specific region, therefore generalizability may be limited compared to multicenter studies. Moreover, the sample size is small and although the rate of vaccination in second and third trimesters are similar, the rate in the first trimester remains too small for any further interpretation.

5. Conclusions

In this study, COVID-19 vaccination in pregnancy was not associated with significant adverse perinatal outcomes. Vaccine uptake rate was below the average global vaccine uptake rates. In order to increase COVID-19 vaccine uptake, policymakers and healthcare professionals should use effective media campaigns and public health messages to inform target populations about the safety of vaccination and reduce the mistrust in the efficacy of available vaccines. Overall, COVID-19 infection was not associated with increased adverse perinatal outcomes. Our results should be confirmed in a bigger cohort in order to draw more definite conclusions.

Availability of Data and Materials

The data supporting the findings of this study is available via OSFHOME data repository https://osf.io/mjquk/ with DOI number 10.17605/OSF.IO/MJQUK.

Author Contributions

MD, IK and MM designed the research question. AC, IU, ZS, SC, EY, CK joined MD and IK with drafting the manuscript and data acquisition. MD, IK and MM have done the critical review. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Local Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey has approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.G.P.0.01/354). The study protocol was maintained in accordance with the Declaration of Helsinki, and informed consent was obtained from all the participants.

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Conflict of Interest

The authors declare no conflict of interest.

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