


CLINICAL ARTICLE

Obstetrics

The association of maternal SARS-CoV-2 vaccination-to-delivery interval and the levels of maternal and cord blood antibodies

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Abstract

Objective: To evaluate the correlation of maternal and cord blood levels of SARS-CoV-2 antibodies in pregnant women immunized against COVID-19.

Methods: A prospective cohort study was performed of pregnant women who delivered at a single university affiliated tertiary medical center. Women who received the COVID-19 vaccine (BNT162b2 Pfizer©) were approached. The correlation between levels of maternal sera and umbilical cord SARS-CoV-2 specific IgG was assessed.

Results: Overall, 58 women were included; of them, 19 had received a single dose and 39 received two doses of the COVID-19 vaccine. Positive levels of umbilical cord IgG were found in 13/19 (68.4%) and 38/39 (97.4%) women after the administration of a single dose and two doses of the vaccine, respectively. The levels of SARS-CoV-2 IgG antibodies in the maternal sera of vaccinated women were positively correlated to their respective concentrations in cord blood sera ($\rho = 0.857$; R^2 linear = 0.719; $P < 0.001$). Thirteen days after vaccination, the ratio of maternal-to-umbilical cord anti Spike IgG antibodies was approximately 1, indicating relatively similar levels in maternal and cord sera.

Conclusion: After the SARS-CoV-2 vaccine, levels of maternal and cord blood antibodies were positively correlated, especially when tested after 13 days following administration of the first dose of the vaccine.

KEYWORDS

antibodies, cord blood, SARS-COV-2, vaccination

1 | INTRODUCTION

In December 2020, the U.S. Food and Drug Association (FDA) approved the messenger ribonucleic acid (mRNA)-based vaccine against SARS-CoV-2, developed by Pfizer© (Pfizer Inc., New York,

NY, USA). In this setting, Israel has become one of the world's leaders, thanks to its rapid vaccination policy and the "top bottom" healthcare structure.¹

Pregnant women are at greater risk for severe complications related to COVID-19 compared to the non-pregnant

population,^{2,3} with the Centers for Disease and Control and Prevention (CDC) including pregnancy as one of the factors associated with increased risk for severe COVID-19 illness.⁴ Infants and neonates are also reported to be more susceptible to critical illness.⁵

However, since the safety and efficacy of the mRNA COVID-19 vaccine was not well studied in the general obstetric population,⁶ data are lacking with regard to maternal humoral response to it. Moreover, studies regarding the efficacy of the mRNA COVID-19 vaccine for adequate production of maternal antibodies and the association with levels of cord blood antibodies are scarce.

Despite these uncertainties, 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 from pregnant women.⁷

Prior studies addressing this issue have reported efficient transplacental transfer of IgG to the infant. However, available studies were limited by small sample size,⁸⁻¹⁰ homogenous population,⁸ and lack of data regarding adverse effects and neonatal outcomes.^{8,10} Finally, limited information exists regarding the interval from maternal vaccination to delivery that is associated with adequate levels of cord blood antibodies, which can assist in planning the optimal timing of maternal vaccination before delivery.

Thus, the aim of the present study was to evaluate the correlation of maternal and cord blood sera SARS-CoV-2 antibodies levels in pregnant women immunized against COVID-19, to estimate an ideal time for vaccination to achieve adequate levels of antibodies in fetal sera, and to evaluate adverse effects after administration of the vaccine in pregnancy.

2 | METHODS

2.1 | Study design

A prospective cohort study was conducted of pregnant women who delivered at a single university affiliated tertiary medical center in Tel Aviv, Israel from December 2020 to March 2021.

Women with a singleton pregnancy and aged 18–45 years who received the COVID-19 vaccine (BNT162b2 Pfizer©) were approached. Exclusion criteria were: (1) unverified timing of vaccination; (2) prior or active infection with COVID-19; and (3) refusal to sign an informed consent form.

The present study was approved by the Institutional Review Board of the Tel-Aviv Sourasky Medical Center (1092-20-TLV; approval date December 29, 2020) and was registered as NCT04724642.

2.2 | Participants and procedure

All women who received the mRNA COVID-19 vaccine (BNT162b2; manufactured by Pfizer©) during pregnancy were recruited in the delivery room via random questioning.

Demographic and clinical information were collected from the electronic medical records. Adverse effects from the vaccination were self-reported.

All participants reported they had not had prior COVID-19 infection, which was further validated via serologic testing for the anti-nucleocapsid antibodies. Current infection was excluded using polymerase chain reaction (PCR) nasopharyngeal swabs at the time of admission, routinely taken for all parturients.

2.3 | Sample collection

Maternal blood was collected from each participant during delivery and umbilical vein blood was collected after delivery and before placental detachment. Both blood samples were centrifuged at 400 g for 10 min at room temperature and the sera were stored at -80°C (-112°F).

2.4 | Serological assays

Humoral response was evaluated by measuring anti-nucleocapsid IgG antibodies and anti-SARS-CoV-2 spike receptor binding domain (RBD; anti Spike IgG) titers.

Maternal and cord sera were analyzed using quantitative chemiluminescent microparticle immunoassay (CMIA) of anti-SARS-CoV-2 spike RBD IgG antibodies (SARS-CoV-2 IgG II; Quant, Abbott, Ireland) and qualitative chemiluminescent microparticle immunoassay (CMIA) of anti-nucleocapsid IgG antibodies (SARS-CoV-2 IgG, Abbott, Ireland).

Cord sera were further analyzed for anti-SARS-CoV-2 spike RBD IgM antibodies (VIDAS[®] SARS-CoV-2 IgM; bioMérieux, France) (anti Spike IgM).

Anti-spike IgG antibodies were provided in arbitrary units (AU/ml) in the range of 0–40000. Levels of 50 AU/ml and above were considered positive.¹¹ Anti-nucleocapsid IgG antibodies were provided in relative light units (RLU). Levels above 1.4 RLU were considered positive.¹² Anti-spike IgM antibodies were interpreted as negative when *i* was less than 1.00 and positive when *i* was 1.00 or above.¹³

2.5 | Statistical analysis

The demographic and obstetrical characteristics of the population cohort were described. Additionally, timing and reported adverse effects were reported.

Levels of anti-spike IgG were transformed to log₁₀. The correlation between maternal sera and levels of umbilical cord anti-spike IgG were assessed by Spearman test.

Curved regression analysis (quadratic model) was used to assess the association between the levels of log₁₀ transformed anti-spike IgG in umbilical cord and the time interval from administration of the first dose of the COVID-19 vaccine to delivery (regression line as

well as 95% confidence interval to mean are presented). This model provided the best fit for the data.

The cohort was further stratified by the level of umbilical cord blood anti-spike IgG antibodies. Characteristics of cases with levels above 50 AU/ml were compared to those with levels below 50 AU/ml. For univariate comparisons, χ^2 test or Fisher exact test were used for categorical variables, and Student t-test or Mann-Whitney U-test were used for continuous variables.

The predictive values of time elapsed from first dose to delivery in predicting umbilical cord blood level of anti-spike IgG antibodies of 50 AU/ml or greater were calculated, using the cutoff of 14 days or more.

Hypotheses were tested using two-tailed tests with a significance level of 0.05. All statistical analyses were performed using the statistical software SPSS version 27 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

During the study period, 58 women who were vaccinated against COVID-19 met the inclusion criteria. Of them, 19 were vaccinated with only a single dose and 39 received two doses of the COVID-19

TABLE 1 Demographic and obstetrical characteristics of the study cohort^a

Demographic and obstetrical characteristics (n = 58)	
Maternal age (years)	32.0 (30.0–35.0)
Pre-pregnancy BMI ^b	23.0 (20.0–24.0)
BMI \geq 30	2 (3.6)
Smoking	0
Nulliparity	25 (43.1)
Labor and delivery characteristics	
Maternal	
Gestational age at delivery (weeks)	39.0 (38.0–39.2)
Preterm delivery (<37 weeks)	2 (3.4)
Mode of delivery	
Vaginal delivery	50 (86.2)
Operative vaginal delivery	5 (8.6)
Cesarean delivery	3 (5.2)
Maternal hospitalization length (days)	2.0 (2.0–2.0)
Neonatal	
Female sex	29 (50.0)
Birth weight (g)	3200 (2911–3448)
Apgar 5 min <7	0
Admission to NICU	1 (1.7)
Neonatal length of hospitalization (days)	2.0 (2.0–2.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; IQR, interquartile range; NICU, newborn intensive care unit.

^aValues are given as number (percentage) or median (IQR).

^bN for BMI was 56.

vaccine (doses were given 21 days apart as per the national protocol for vaccination).

3.1 | Characteristics of participants

The demographic, obstetrical, and neonatal characteristics of the study cohort are presented in Table 1.

3.2 | Characteristics of the vaccine

The characteristics of the vaccine and reported adverse effects are detailed in Table 2. The median gestational age at administration of the first dose of the vaccine was 34.5 weeks (range 33.0–36.0 weeks) and median first vaccine dose-to-delivery interval was 30.0 days (range 19.7–40.5 days). Overall, 28 of 58 women (48.2%) reported at least one adverse effect after the first dose of the vaccine (Table 2).

Of the women, 39 (67.2%) received both the first and second doses of the vaccine before delivery. The median gestational age at administration of the second dose of the vaccine was 37.0 weeks (range 36.0–38.0 weeks) and the median second vaccine dose-to-delivery interval was 15.0 days (range 8.0–23.0 days). Adverse effects were reported by 20 of 39 (51.2%) women after the second dose of the vaccine (Table 2). Comparing adverse effects after the first and second doses failed to show significance ($\chi^2 P = 0.706$).

3.3 | Transplacental transfer of antibodies

Levels of SARS-CoV-2 anti-spike IgG in maternal sera were positively correlated to their respective concentrations in cord blood sera ($\rho = 0.857$; R^2 linear = 0.719; $P < 0.001$; Figure 1).

Anti-nucleocapsid IgG was negative in all samples of maternal and umbilical cords, indicating that all women did not acquire COVID-19 infection before delivery. In addition, anti-spike IgM antibodies were negative in all samples of umbilical cord, confirming that no active immunity was induced in the fetus.

3.4 | Correlation between time interval from first dose to delivery and levels of anti-spike IgG

The correlation of the time interval from the first dose of the vaccination with levels of umbilical anti-spike IgG cord sera was further assessed. In the overall group (n = 58), levels of anti-spike IgG in the umbilical cord sera were initially positively correlated to the time interval from first dose to delivery, with an apparent plateauing at approximately 35–40 days after administration of the first dose (Figure 2).

In order to better evaluate the effect of time on the correlation between levels of maternal sera and umbilical cord IgG, maternal to umbilical cord anti-spike IgG antibodies were calculated and this

TABLE 2 Characteristics and adverse effects of the vaccination in the study cohort^a

	First dose of vaccine	Second dose of vaccine
Gestational age at vaccination (weeks)	34.5 (33.0–36.0)	37.0 (36.0–38.0)
Dose-to-delivery interval (days)	30.0 (19.7–40.5)	15.0 (8.0–23.0)
Overall women with any maternal adverse effects after vaccination	28/58 (48.2)	20/39 (51.2)
Enhanced fetal movements perception	1 (1.7)	0
Pain at injection site	14 (24.1)	8 (20.5)
Back pain	2 (3.4)	0
Fatigue/weakness	9 (15.5)	9 (23.0)
Chills	3 (5.1)	5 (12.8)
Myalgia	3 (5.1)	5 (12.8)
Fever	0	1 (2.5)
Headache	5 (8.6)	2 (5.1)
Peripheral facial nerve paralysis	1 (1.7)	0
Nausea	1 (1.7)	0
Dizziness	1 (1.7)	1 (2.5)
Unspecified illness	3 (5.1)	4 (10.2)

Abbreviation: IQR, interquartile range.

^aValues are given as number (percentage) or median (IQR).

ratio was assessed as function of time from first dose to delivery. While during the first 13 days the ratio was >1 , indicating high levels of maternal antibodies compared to levels in the cord blood sera, the ratio was approximately 1 after the first 14 days from the administration of the first dose and remained relatively similar afterward (indicating similar levels of maternal and cord blood antibodies levels) (Figure 3).

When comparing those testing positive for umbilical cord anti-spike IgG antibodies (level ≥ 50 AU/ml; $n = 51$) with those testing negative (level < 50 AU/ml; $n = 7$), a higher median interval was found from first vaccination to delivery in the positive antibodies group (34.0 [24.0–43.0] vs. 12^{10–13}; $P < 0.001$) (Table 3).

Of those with umbilical cord anti-spike IgG levels below 50 AU/ml, all had a first dose-to-delivery interval of 13 days or less, except one woman who had an interval of 26 days. The predictive indices were calculated of this cutoff (14 days) for the prediction of positive levels of umbilical cord blood anti-Spike IgG (≥ 50 AU/ml). This cutoff was associated with a sensitivity of 85.7% (95% confidence interval [CI] 42.1–99.6), specificity of 96.0% (95% CI 86.5–99.5), positive predictive value of 75.0% (95% CI 42.7–92.3), and a negative predictive value of 98.0% (95% CI 88.8–99.6) (Table 4).

4 | DISCUSSION

The aim of the present study was to explore the association of maternal and cord blood sera SARS-CoV-2 antibodies in women vaccinated against COVID-19 during pregnancy and to assess the association of antibody levels with the interval from the administration

of the first dose of vaccine and delivery. The main findings of the study were: (1) there was good correlation between levels of maternal sera and umbilical cord SARS-CoV-2 anti-spike IgG; (2) the levels of anti-spike IgG in umbilical cord follow quadratic behavior, and significantly correlated with the time interval from the administration of the first dose of the vaccine; and (3) positive levels of anti-spike IgG antibodies in the umbilical cord (≥ 50 AU/ml) can be achieved from 13 days after administration of the first dose.

4.1 | Results of the study in the context of other observations

Since the emergency-use authorization (EUA) by the FDA for the three mRNA COVID-19 vaccines, there has been substantial need for research regarding efficacy and safety in pregnant and neonatal populations.¹⁴ Furthermore, data are lacking regarding the degree of transplacental passive immunity in vaccinated or infected women.^{15,16} According to Edlow et al.,¹⁵ the transplacental transfer in naturally immunized women is insufficient, as opposed to Flannery et al.,¹⁶ who demonstrated adequate transmission. The findings of the present study support recent data regarding the role of vaccination in pregnant women to induce both maternal and neonatal immunity.^{8–10}

Early on in life, immune protection is accomplished by the transferring of maternal antibodies from mother to offspring.¹⁷ Since the data implicate increased neonatal vulnerability to COVID-19 infection,¹⁸ major concern has risen, and reinforcement of prevention efforts has become a subject of great interest. Efficient placental transfer of IgG antibodies was found in vaccinated women as well as a positive correlation between maternal and umbilical cord antibody

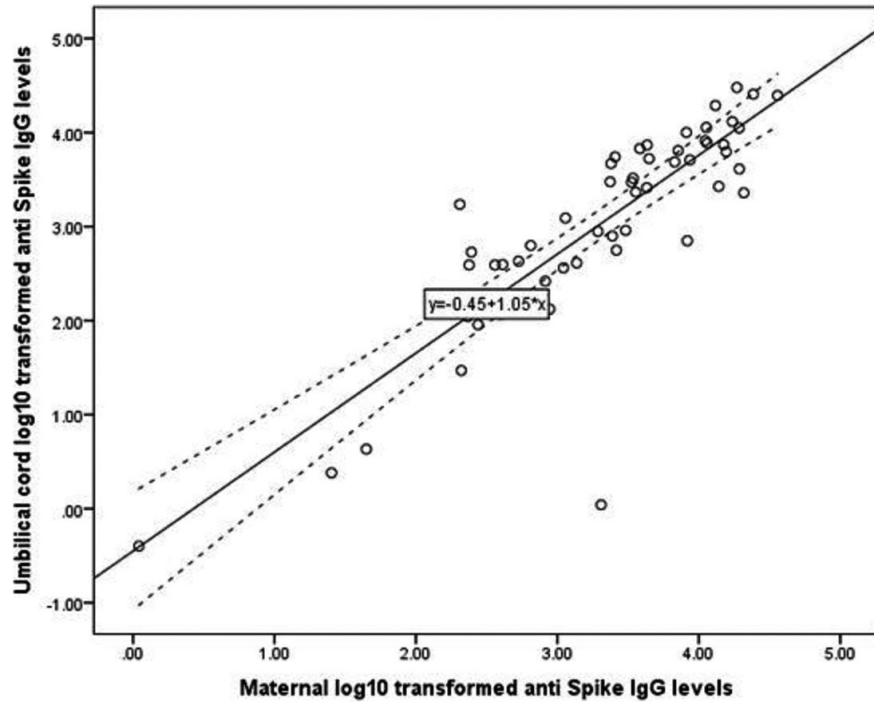


FIGURE 1 Correlation between levels of maternal sera and umbilical cord SARS-CoV-2 IgG. Levels of SARS-CoV-2 log₁₀ transformed anti-spike IgG in maternal sera were positively correlated to their respective concentrations in cord blood (Spearman $\rho = 0.857$; R^2 linear = 0.719; $P < 0.001$). Regression line of the mean (solid line) and 95% confidence interval (CI) (dotted lines) are presented

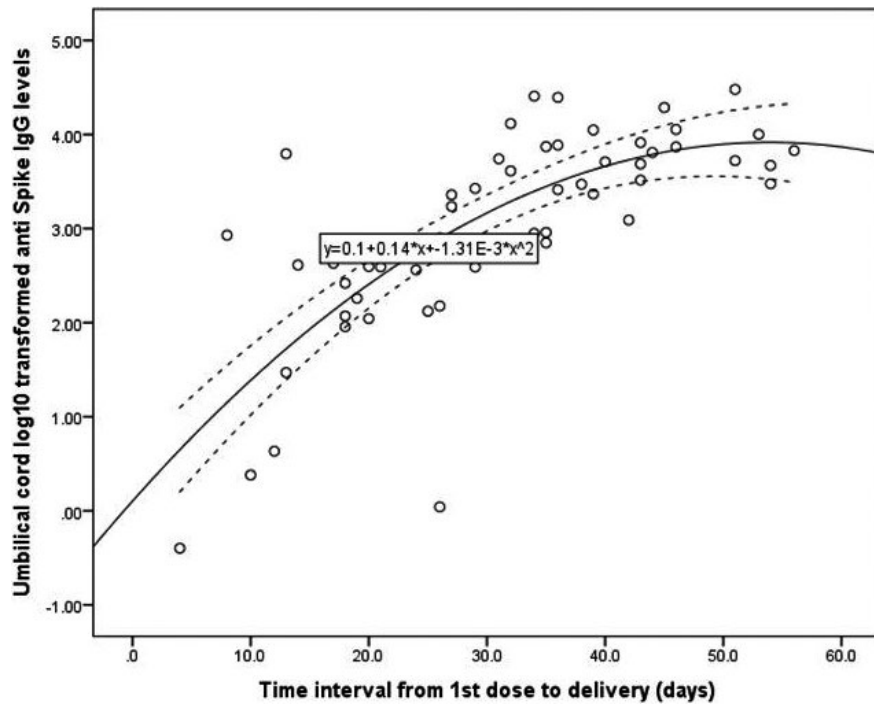


FIGURE 2 The association of the time interval from the first dose of vaccine to delivery and levels of cord blood anti-spike IgG. The levels of SARS-CoV-2 log₁₀ transformed anti-spike IgG in umbilical cord as a function of time interval from administration of the first dose of the COVID-19 vaccine to delivery is presented (Spearman $\rho = 0.768$; R^2 quadratic = 0.568; $P < 0.001$). Regression line of the mean (solid line) and 95% confidence interval (CI) (dotted lines) are presented. Mean (solid line) and 95% CI (dotted lines) are presented

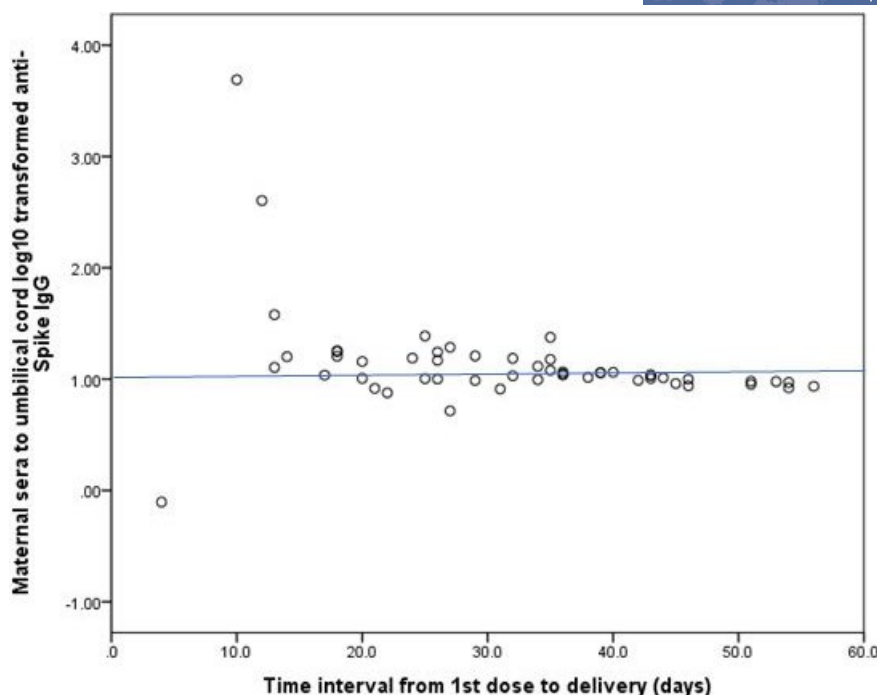


FIGURE 3 Ratio of maternal sera to umbilical cord of SARS-CoV-2 anti-Spike IgG. SARS-CoV-2 log₁₀ transformed anti-spike IgG maternal sera to umbilical cord as a function of time interval from administration of first vaccine dose to delivery. Within the first 2 weeks, the ratio is more than 1. However, after 2 weeks the ratio is around 1 (Mann–Whitney *U*-test failed to show the significance between the values of this ratio within the first 2 weeks to the following period (>2 weeks); *P* = 0.104)

TABLE 3 SARS-CoV-2 specific antibodies stratified by the level of anti-spike IgG in umbilical cord^a

	Umbilical cord anti-spike <50 AU/ml (n = 7)	Umbilical cord anti-spike ≥50 AU/ml (n = 51)	<i>P</i> value
Two vaccine doses were administrated	1 (14)	38 (74)	0.002
First vaccine dose to delivery interval (days)	12 (10–13)	34 (24–43)	<0.001
Maternal sera anti-spike IgG levels	25.3 (1.1–209.2)	3386.3 (777.9–11 340.4)	<0.001
Maternal sera anti-spike IgG levels <50 AU/ml	5 (71)	1 (2.0)	<0.001
Umbilical cord anti-spike IgG levels	1.1 (0–4.3)	2594 (428.3–6757.6)	<0.001

Abbreviation: IQR, interquartile range.

^aValues are given as number (percentage) or median (IQR).

TABLE 4 Predictive values for time interval for SARS-CoV-2 anti-spike specific IgG umbilical cord immunity

	Value	95% CI
Sensitivity (%)	85.71	42.13–99.64
Specificity (%)	96.08	86.54–99.52
Positive likelihood ratio	21.86	5.43–87.91
Negative likelihood ratio	0.15	0.02–0.91
Accuracy ^a	94.83	85.62–98.92

Abbreviation: CI, confidence interval.

^aThese values are dependent on disease prevalence.

concentrations. Another encouraging finding is the relatively high placental transfer ratio of 1, which is consistent with the range of 0.84–1.7 that has been reported for other vaccine-elicited antibodies such as Hepatitis B, rubella, measles, influenza, and pertussis.^{19–21}

In the present cohort, the levels of anti-Spike specific IgG in the umbilical cord sera were initially positively correlated to the time interval from first dose to delivery, but an apparent plateauing after approximately 35–40 days was noticed. It is unclear whether a decrease in the levels of antibodies after this period should be expected as the cohort did not include women who were vaccinated more than 55 days before delivery. It is apparent that further studies on this subject are greatly needed.

The safety profile for pregnant women is of great concern, and one of the barriers preventing pregnant women from getting vaccinated.²² The present study did not reveal any alarming adverse effects, similar to the data published in recent studies that evaluated vaccine safety in pregnant women.^{9,14,23} In accordance with prior studies, it was discovered that the most common maternal adverse effect was pain at the site of injection. No major neonatal adverse effects were detected in the present study, similar to the results of Shimabukuro et al.,¹⁴ who demonstrated spontaneous abortion as the most common adverse

effect. This result should be interpreted with caution since the women in the present study were vaccinated in the third trimester and were recruited to the study upon entry to the delivery room.

Another worthy fact to note is the time interval from administration of the first dose to the achievement of adequate cord immunity. According to previous studies,^{8,10} such an interval exists, and more neonates acquire immunity as time elapses, although a specific cutoff was not calculated. This interval was found to be 13 days, regardless of administration of the second dose. This finding is in accordance with a recent study that showed that an interval of 14 days after a single dose of the vaccine provides immunity against severe disease.²³ A trend towards a plateau in the level of anti-spike IgG antibodies as time elapses after the first dose of the vaccine was also found. A time interval from vaccination to neonatal immunity is important to define the optimal timing of vaccination in pregnant women. Although vaccinating pregnant women is important throughout pregnancy to decrease maternal morbidity, with the hopeful dwindling of the disease in various parts of the world subsequent to vaccination, it may be possible to schedule appropriate vaccination during pregnancy to enhance neonatal immunity. Whether maternal immunity waxes or wanes as the time from vaccination increases may also be discovered.

4.2 | Strengths and limitations

The present study has several strengths. First, while previous studies examined antibodies in infected pregnant women with only limited data regarding vaccinated pregnant women and their placental transfer, the present study focused on women who were vaccinated against COVID-19.

Second, the entire cohort was naïve to the SARS-Cov-2 virus as demonstrated by the absence of positive IgG nucleocapsid antibodies in all women. Furthermore, IgM antibodies in all umbilical cord samples were examined in order to ensure the examination of passive versus active immunity in neonates. Lastly, all women in the present cohort were vaccinated with the same type of vaccine (Pfizer), thereby increasing the validity of the study results.

The present study has some limitations. Only antibody titer was examined, and not the quality of the antibodies, as may be detected by testing neutralizing antibodies. However, recent data suggest anti-spike IgG can serve as a surrogate marker for virus-neutralizing activity.²⁴ In addition, all women in the present cohort were vaccinated in the third trimester of pregnancy, a fact that limits the knowledge about the immunity afforded by vaccinations earlier on in pregnancy. Finally, although the present study is the largest to date examining umbilical cord SARS-CoV-2 antibodies in pregnant vaccinated women, the sample size comprised only 58 women.

5 | CONCLUSION

In conclusion, it was demonstrated that vaccination with the mRNA SARS-Cov-2 vaccine has an adequate maternal and obstetric safety

profile, in addition to affording maternal and neonatal quantitative immunity. Therefore, and in light of the pandemic that began in December 2019, consideration of vaccination during pregnancy worldwide is recommended, in accordance with results to be obtained in future large prospective studies.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors had substantial contribution to this study and gave their final approval of this version to be published. All authors agreed to be accountable for all aspects of the study.

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