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Identification of the “Spike” protein in umbilical cord blood of newborns from mothers vaccinated for SARS-CoV-2 during pregnancy.

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Abstract

OBJECTIVE: Identification of the presence of SARS-CoV-2 *Spike* protein antibodies in umbilical cord blood of newborns following maternal COVID-19 vaccination during pregnancy.

MATERIALS AND METHODS: Cross-sectional study in women vaccinated for SARS-CoV-2 during pregnancy who had a cord blood sample taken during the pregnancy termination surgical procedure (Vaginal birth/Cesarean section) to measure spike protein antibodies, at a private medical center in Mexico City, between June 2021 and February 2022.

RESULTS: We registered 219 patients in the study: five types of vaccines from two different platforms were tested: Pfizer®, Moderna®, AstraZeneca®, J&J/Janssen® and Sputnik®. The levels of antibodies were greater in those patients vaccinated with Moderna® and Sputnik®. A predictive model was evaluated with Cox regression analysis, and no significant statistical differences were found in the number of antibodies generated after the first and second vaccine dose.

CONCLUSIONS: Prenatal vaccination against COVID-19 induces a strong maternal humoral response that is effectively transferred to the fetus, even with a single dose.

KEYWORDS: SARS-CoV-2; Pregnancy; *Spike* protein; Passive immunity; Vaccination.

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BACKGROUND

Less than a year had passed after the identification of the severe acute respiratory syndrome caused by the SARS-CoV-2 which leads to COVID-19, and effective vaccines were being distributed globally, with the aim of ending the COVID-19 pandemic.¹ During that time, several vaccines were developed to prevent COVID-19. With reported efficacies between 90-95%, they were initially given to priority groups, such as health care personnel and the elderly population. However, pregnant women, or in lactation, were excluded, and continue to be excluded, from these protocols, and there is still little evidence of their safety and efficacy.

Confirmed infection by SARS-CoV-2 was the main cause of maternal death during the years 2020 and 2021 (21.6 and 42.7%, respectively), and it is estimated that globally, the number of infected pregnant women surpasses millions of cases.²⁻⁴ The current information suggests that infected pregnant women are at greater risk of admission to the intensive care unit, requiring invasive ventilation and extracorporeal membrane oxygenation (ECMO), and of a higher rate of mortality in comparison with non-pregnant women. The effects of vaccination for COVID-19 in the fetus are not fully understood. Intrauterine infection occurs, but it is rare. There is even an association between COVID-19 infection and pre-term birth, with a threefold higher risk in women who present symptoms of the disease.⁵⁻⁶ Even with the knowledge of these risk factors, most pregnant women have been reluctant to vaccination against the virus, due to safety issues. Moreover, an immune response and a maternal antibody transfer through the placenta have been shown, with a possible passive immunity for the newborns of mothers infected with SARS-CoV-2 during pregnancy. Likewise, antibodies specific to the vaccine have been found in the umbilical cord after 15 days of the first dose of the messenger RNA (mRNA) vaccine,² which suggests

that vaccination can provide newborns with some protection against COVID-19.

According to the action mechanisms of mRNA, and the viral vector of the vaccines, some authors point out that it is unlikely that the vaccination poses a risk to pregnant women, fetuses, or newborns,⁷⁻¹¹ so the recommendation is to vaccinate all pregnant women. Patients with higher exposure, or at risk of severe infection (diabetes, obesity, or hypertension) can benefit the most from it.¹²⁻¹³ The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine, have emitted guidelines to promote vaccination in pregnant women.¹²⁻¹⁴

Pregnancy is a condition to take into account regarding how the immunity per trimester, and the vaccines against COVID-10, can interact to protect the mother and the child.¹⁵ Because of the reactogenicity of the vaccine (fever), especially during the first trimester of pregnancy, the risk of defects in the neural tube, or of a congenital alteration, can increase.^{1,7} However, these kind of risks in pregnant women and the fetus, have to be pondered against the risks of COVID-19. The availability of multiple vaccines in Mexico gives the opportunity to examine how the vaccine platforms, and the moment of vaccination during the pregnancy, affect neonatal immunity.

Based on the aforementioned, the goal of this study was to identify the coexistence of antibodies against the protein "Spike" of SARS-CoV-2 in the umbilical cord blood of newborns of mothers vaccinated for COVID-19 during pregnancy.

MATERIALS AND METHODS

Cross-sectional study, conducted in patients seen at the Obstetrics and Gynecology Department at the ABC Medical Center. The sample was taken by convenience, including pregnant patients

with a complete vaccination for SARS-CoV-2, and newborns from vaccinated mothers between June 2021 and February 2022. *Inclusion criteria:* women 18 and older, with complete clinical records, who had received a full vaccination scheme for SARS-CoV-2 during pregnancy, and from whom, at the time of birth (vaginal or C-section), a blood sample from the umbilical cord of the newborn was taken, as indicated by the physician in charge, to identify the Spike protein. At the time of the study, there were 2 messenger RNA vaccines (Pfizer® and Moderna®), 2 adenovirus vaccines (Janssen Biotech® and Sputnik V®), and one related to the viral vector (AstraZeneca®). The samples were analyzed with the Roche Diagnostics platform and reactive, authorized by the FDA. The electrochemiluminescence immunoassay (ECLIA) reported quantitative and qualitative results, considering any result equal or above 1 as positive, with a maximum value of 2500 U/mL. *Exclusion criteria:* patients with COVID-19 at the termination of pregnancy, women with an incomplete vaccination scheme, or who had received a third dose, or “boost”.

The clinical and demographic information, including the type of vaccine and time of administration were obtained from electronic clinical records of the TIMSA Laboratory. The descriptive and statistical analysis were made with the Statistical Package for the Social Sciences (SPSS) software. The concentration of antibodies per vaccine was reported, as well as the dosage, and the trimester of scheme completion. The non-parametric test of Kruskal-Wallis was used for the analysis of ordinal variables. The test determined if the medians of the analyzed groups were different. A value of $p < 0.05$ was considered statistically significant. A predictive model was made with Cox regression, to analyze the effect of the number of total antibodies after the first and the second vaccination dose. The study was approved by the Research Committee and the ABC Medical Center Research Ethics Committee, number TABC-23-83.

RESULTS

Two hundred and thirty-one samples of total antibodies from newborn umbilical cord blood were obtained from mothers vaccinated against COVID-19 during pregnancy. However, only the samples from mothers with complete vaccination schemes were included ($n = 219$), and the samples of mothers who had received a third dose were excluded ($n = 12$). From the patients with a complete vaccination scheme, 6 twin pregnancies were reported (2.73%), from whom a sample was obtained from each cord. The demographic characteristics of the pregnant women with full vaccination schemes against SARS-CoV-2 is shown in **Table 1**.

From the vaccines included in the study, the mRNA ones were the most prevalent, with 155 patients vaccinated with Pfizer®, and 41 with Moderna®. From the vector vaccines, 6 patients received AstraZeneca®, 9 J&J/Janssen®, and 8 Sputnik®. The minimum value reported by the laboratory was 0.00 UI/mL, and the maximum was 2500 UI/mL. The characteristics of the vaccination scheme and the antibody titration are shown in **Table 2**.

According to the non-parametric Kruskal-Wallis test, there were statistically significant differences between the antibody concentration and the type of vaccine, with a higher median and distribution for Moderna® and Sputnik® (average limits of 123.18 and 176.25; $p = .005$), in comparison with the other vaccines. **Figure 1**

Most of the patients completed their corresponding vaccination scheme on the second (59.36%; $n = 130$), and third (28.31%; $n = 62$) trimesters, followed by the first (12.32%; $n = 27$), as shown in **Table 3**. The non-parametric Kruskal-Wallis test was used to compare the antibody concentrations by trimester when the scheme was completed. The average upper limit was for the third trimester, and the lower for the first, with a

**Table 1.** Demographic characteristics of study population

Variable	Mean
Age (years)	32.9
Pregnancies	2
Singleton pregnancy	213 (97.26%)
Twin pregnancy	6 (2.73%)
Weeks of pregnancy	38.5
Vaccine	
Pfizer®	70.77 %
Moderna®	18.72 %
AstraZeneca®	2.73 %
J&J/Janssen®	4.10 %
Sputnik®	3.65 %
Newborns	
Female	108 (47.94 %)
Male	117 (52.05 %)
Fetal weight (g)	2,991.26

The data is expressed as means (SD) and percentage, and qualitative variables in absolute frequencies (%).

statistically significant difference, and we found that there were higher results for antibody concentrations during the third trimester (average limit 147.06; $p = .000$). **Figure 2**

For patients who required two doses to complete the scheme because of the type of vaccine, a

predictive model was calculated with a Cox regression, where the effect of the total antibody concentrations for the first and the second dose was analyzed. **Figures 3 and 4** don't show differences between the antibodies with the first and second doses .

DISCUSSION

Throughout history, crises in public health have accelerated the discovery and development of vaccines, and the COVID-19 pandemic was no exception. The transplacental transmission of IgG after vaccination against tetanus, influenza, and whooping cough provides protection for newborns. It has even been observed that vaccination against COVID-19 during pregnancy can provide some protection against the disease.¹⁶⁻¹⁷

There is a higher efficacy in the immune response and in the transmission of antibodies with mRNA vaccines than with viral vectors.^{15,18-19} The first countries to administer the vaccine against COVID-19 during pregnancy (United States and Israel) used biological with mRNA (Pfizer® and Moderna®), and the first available data was about these vaccines. As a result, when other

Table 2. Characteristics by vaccine

Characteristics	Pfizer®	Moderna®	AstraZeneca®	J&J/Janssen®	Sputnik®
Vaccinated women (n)	155	41	6	9	8
IgG in umbilical cord blood (mean; CI95%)	1306.15 (1164.58 - 1447.72)	1536.53 (1275.31 - 1797.76)	898.00 (2.13 - 1793.86)	987.70 (102.94 - 1872.45)	2272.75 (1735.38 - 2810.11)
Patients with negative antibodies	2	-	-	-	-
Minimum value (UI/mL)	-	283.00	115.00	35.30	682.00
Maximum value (UI/mL)	2500.00	2500.00	2500.00	2500.00	2500.00
Median (UI/mL)	1057.00	1563.00	572.00	274.00	2500.00
Average range	106.13	123.18	79.25	78.25	176.25

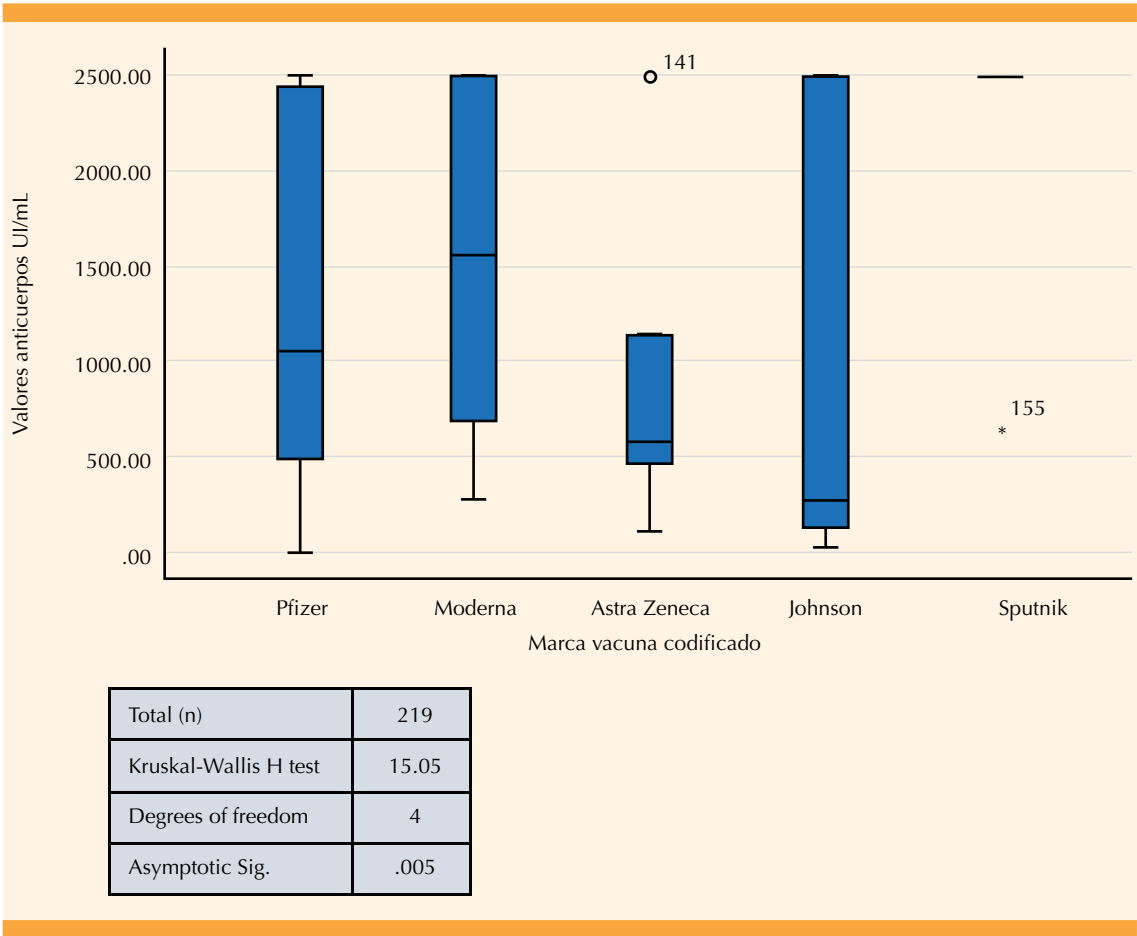


Figure 1. Kruskal-Wallis test. Anti-SARS-CoV-2 antibody concentration (UI/mL) in umbilical cord blood by vaccine.

Table 3. Values per trimester when vaccination scheme was completed

Trimester	Vaccinated women (n)	IgG in umbilical cord blood (mean)	Patients with negative antibodies	Minimum value (UI/mL)	Maximum value (UI/mL)	Median (UI/mL)	Average range
First trimester (CI95%)	27	1012.77 (701.03 - 1323.61)	1	0.00	2500.00	708.00	87.13
Second trimester (CI95%)	130	1170.24 (1022.59 - 1317.88)	1	0.00	2500.00	875.50	97.07
Third trimester (CI95%)	62	1910.22 (1699.76 - 2120.69)	-	35.30	2500.00	2500.00	147.06

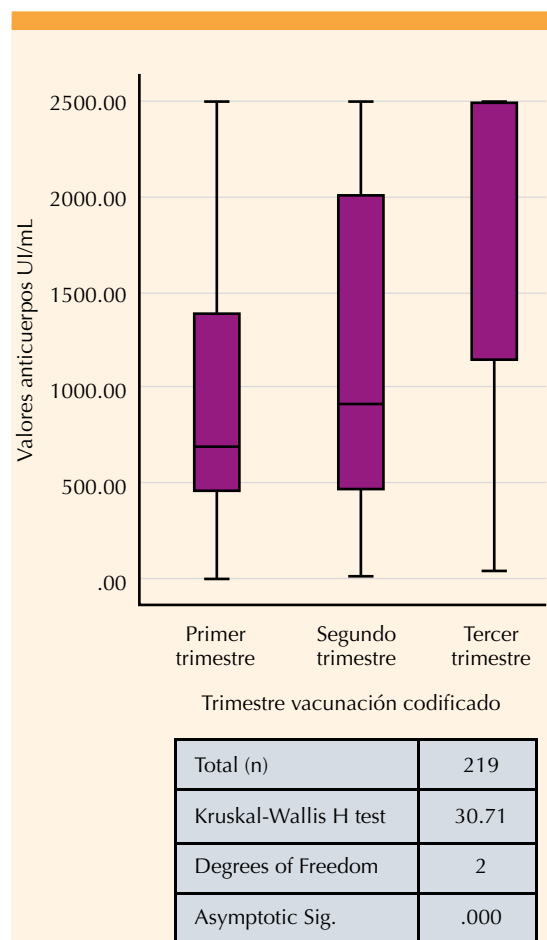
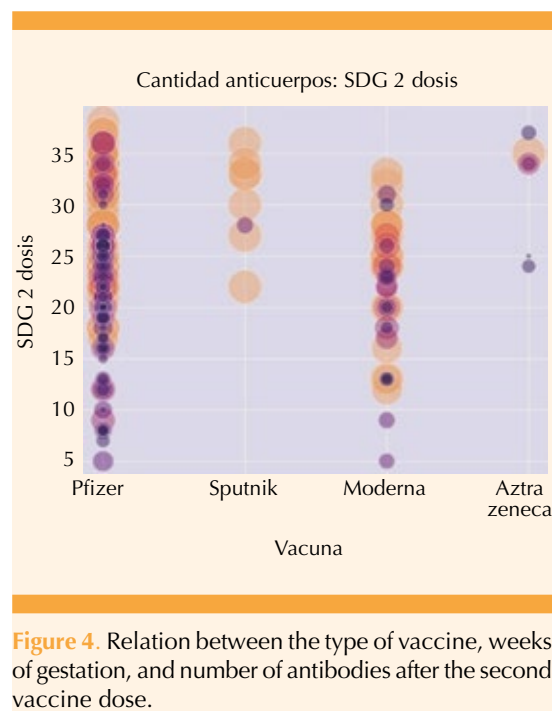
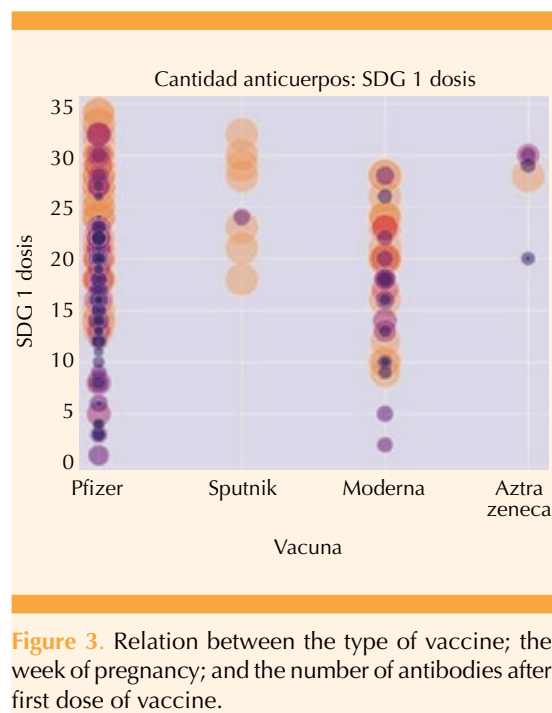


Figure 2. Kruskal-Wallis test. Anti-SARS-CoV-2 antibody concentration (UI/mL) in umbilical cord blood by trimester when vaccination scheme was completed.

countries had the vaccines available for pregnant women, they offered primarily mRNA vaccines for this type of patients.¹⁶ Even though all of the vaccines generate antibodies against the Spike protein, we observed in our population that the most antibodies were generated in patients vaccinated with Moderna® and Sputnik®, the latter with higher antibody titration (Figure 1). Recent studies highlight the importance of the response mediated by memory T cells in vaccines with



viral vectors, and they show a better neutralizing capacity at 8 months with a single dose, and better protection over time.²⁰⁻²¹

Regarding the optimal time for vaccination, there is variability by trimester and type of vaccine; however, even though most of our population completed the scheme on the second trimester of their pregnancy (59.36%), there was a higher concentration of antibodies in umbilical cord blood of patients who finished their scheme on the third trimester (mean: 1910.22 [CI95:1699.76-2120.69]; **Figure 2**). However, even though the titration of antibodies was lower in patients vaccinated on the first trimester, the booster dose on the third trimester can optimize the transmission of antibodies and generate higher immunity; thus the mRNA vaccines are the most recommended by the CDC, ACOG, and the Society for Maternal-Fetal Medicine.²²⁻²⁴

The results of diverse studies provide a better understanding of the moment when the vaccine has to be administered to pregnant women, the way it can affect the immune response, and the efficiency in transplacental transmission, even of vaccines routinely administered (Influenza, Tdap). For example, the Advisory Committee on Immunization Practices (ACIP) has recommended for a long time, the administration of Tdap after 20 weeks of pregnancy,²⁵ based on the scarce evidence about safety during the first trimester. However, it has been shown that there is a higher transplacental transmission when vaccination occurs between weeks 27 and 36.^{15,26} The current information about the vaccine against influenza, which can be administered at any gestational age, is still under discussion. Some studies suggest lower antibody transmission in the first trimester, and higher in the third, while other studies report a higher transmission in the first trimester, in comparison with the second.²⁷⁻³⁰ Based on the results of the present study, there is higher antibody transplacental transmission on the third trimester.

Most women who completed the vaccination scheme on the third trimester transferred more antibodies, obtained in the umbilical cord blood of the newborns, which is in line with what is previously reported in the literature.³¹⁻³⁴

A new finding was that the Sputnik® vaccine generated higher concentration of antibodies in cord blood in comparison with the rest of the vaccines. Evaluating the number of antibodies generated with the first and the second doses, there were no statistically significant differences, so a single dose can generate an effective immune response and confer passive immunity to the newborn.

The limitations of the study were not having a sample size which is representative of the population, not identifying the patients who had asymptomatic infection during their pregnancy, and not estimating the number of antibodies which are capable of providing protection for the newborn. Further studies are necessary to include a bigger cohort and with a longer term follow-up. However, even though the antibody titration necessary for protecting newborns against COVID-19 is unknown, these findings are a precedent for pregnant women to consider vaccination against COVID-19.

CONCLUSIONS

The fast development and distribution of vaccines against COVID-19 has offered an unprecedented opportunity to improve the understanding of the immunity induced by vaccines during pregnancy. Vaccination against COVID-19 protects pregnant women and it provides a fetal and newborn benefit, as it prevents adverse effects related to severe disease by COVID-19 during pregnancy, and it provides transplacental immunity to newborns. The main benefit of vaccination against COVID-19 during pregnancy is to reduce the risk of associated complications. Thus, the vaccination aims to optimize protection during pregnancy,



more than that of the infant. However, these results show promising evidence for passive immunity against SARS-CoV-2 in newborns, after the vaccination of the mother during pregnancy.

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