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ARTICLE

Absence of SARS-CoV-2 Spike glycoprotein expression in placentas from individuals after mRNA SARS-CoV-2 vaccination

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Current public health initiatives to contain the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic focus on expanding vaccination efforts to include vulnerable populations such as pregnant people. Vaccines using messenger ribonucleic acid (mRNA) technology rely on translation by immune cells, primarily at the injection site. Hesitancy remains among the general population regarding the safety of mRNA vaccines during gestation, and it remains unknown whether the SARS-CoV-2 Spike protein (the product of mRNA vaccines available) accumulates in the placenta after vaccination. Objective: To determine whether Spike protein translation and accumulation occurs in placental tissue in the context of recent mRNA SARC-CoV-2 vaccination during pregnancy. We identified 48 patients receiving one or two doses of mRNA SARS-CoV-2 vaccine during gestation and used immunohistochemistry against SARS-CoV-2 Spike protein in formalin-fixed, paraffin-embedded placental tissue. One placenta, positive for SARS-CoV-2 RNA by in situ hybridization (ISH) was used as positive control. Seven term placentas collected prior to the emergence of SARS-CoV-2 served as negative controls. Eighty one percent of patients in the study group underwent third-trimester delivery; remaining had a first-trimester spontaneous abortion or elective second-trimester termination. Patients received two (52%) or one (48%) vaccine doses during pregnancy, with a median interval between latest dose and delivery of 13 days (range 2–79 days). Most (63%) cases had their latest dose within 15 days prior to delivery. All the placentas in the study and negative control groups were negative for SARS-CoV-2 immunohistochemistry. Six study cases with short vaccine-delivery intervals (2–7 days) were subjected to SARS-CoV-2 ISH and were negative. Our findings suggest that mRNA vaccines do not reach significant concentrations in the placenta given the absence of definitive SARS-CoV-2 Spike protein accumulation in placental tissue. This observation provides evidence supporting the safety of mRNA vaccines to the placental-fetal unit.

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INTRODUCTION

After the recent emergency use authorization of messenger ribonucleic acid (mRNA) vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the US Food and Drug Administration, several healthcare centers have included pregnant individuals in their vaccination efforts. mRNA vaccines against SARS-CoV-2 currently approved include mRNA-1273, co-developed by Moderna (Cambridge, MA, USA) and the National Institutes of Allergy and Infectious Diseases Vaccine Research Center, and BNT162b1 & BNT162b2 codeveloped by BioNTech (Mainz, Germany) and Pfizer (New York City, NY, USA)[1]. There is emerging data on the safety of mRNA and other SARS-CoV-2 vaccines when administered during pregnancy, with similar rates of pregnancy loss, preterm birth, and intrauterine growth restriction to those reported in pre-pandemic times[2]. Professional organizations such as the American College of Obstetricians and Gynecologists and the Society of Maternal-Fetal Medicine recommend offering vaccination against coronavirus disease of 2019 (COVID-19) to pregnant and lactating women[3,4].

Cumulative literature indicates that COVID-19 is associated with an increased risk of maternal and neonatal adverse outcomes[5,6]. COVID-19 placentitis was initially described in a series of 7 placentas, all with detection of SARS-CoV-2 by in situ hybridization, which is characterized by histiocytic intervillositis, extensive perivillous fibrin deposition and trophoblast necrosis[7]. More recently, a systematic review and meta-analysis by Di Girolamo et al. analyzed 56 studies which included 1008 pregnant patients to assess the placental histopathological changes after SARS-CoV-2 infection. Placentas from infected patients had signs of maternal vascular malperfusion (30.7%), fetal vascular malperfusion (27%), acute and chronic inflammation (22.7% and 25.7%, respectively), increased perivillous fibrin (32.7%), and intervillous thrombosis (14.6%)[8]. Interestingly, 17.5% of cases did not present any abnormal pathologic findings. The consequences of these pathologic placental findings on fetal development are still not well understood. However, separate observational studies have reported that stillbirths are significantly more common in women infected during pregnancy when compared to non-infected pregnant women (8.5 per 1000 vs 3.4 per 1000), and others suggest that the rate of vertical transmission can be as high as 5.3%[9,10]. These observations have fueled the rapid evolution and increasing interest in this field, and have recently

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culminated in establishing definitions of placental infection by SARS-CoV-2 developed by the National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH/NICHD)[11]. The definitions of definitive, probable, possible, and unlikely infection are based on the rigor of testing performed to prove active viral replication in the placenta. These were created to improve result interpretation and allow cross-comparisons between studies in both clinical and research settings[11].

Despite the known risks of placental infection and adverse obstetric outcomes in the setting of COVID-19, there is still hesitancy among the population to embrace vaccination against SARS-CoV-2, especially during pregnancy[12,13]. Hesitancy has been in part justified by the unknown risk of vertical transmission of the mRNA component of the SARS-CoV-2 vaccine to the fetus, and the effects of such event in fetal development and outcomes. Our aim is to explore the possibility of SARS-CoV-2 mRNA translation in the placenta by detecting SARS-CoV-2 Spike (S) protein by immunohistochemistry in placental tissue from individuals vaccinated during pregnancy against SARS-CoV-2 using mRNA technology.

MATERIALS AND METHODS

This project (Protocol # 2021P001022) was approved by the Brigham and Women's Hospital Institutional Research Board, and the study was performed in accordance with the Declaration of Helsinki. We conducted a search in the pathology laboratory information system to identify patients that received one or two doses of SARS-CoV-2 mRNA vaccination before delivery, and in which the placenta was submitted for pathology evaluation, between January 1st, 2021, and December 1st. 2021. Patients with a positive SARS-CoV-2 test or symptomatic COVID-19 before delivery were excluded. A control group composed of seven placentas delivered in December 2018 (one year prior to the reported emergence of SARS-CoV-2), was also retrieved.

Clinical characteristics including parental age, parental or pregnancy-related comorbidities, partum and delivery complications and gestational age at time of delivery were retrieved from electronic medical records. Dates of vaccination (first and second dose) were recorded, as well as the interval between complete vaccination status and delivery. Pathologic characteristics of the placenta were obtained from finalized pathology reports. In addition, histologic material, consisting of 4 to 5 Hematoxylin & Eosin stained slides per case, was reviewed by two authors (AS and CPH) to confirm reported findings.

Immunohistochemistry

One block containing macro and microscopically unremarkable formalin-fixed, paraffin-embedded placental parenchymal tissue was selected in each case and control for immunohistochemical analysis. Immunohistochemistry was performed on 4-µm thick sections from the selected blocks following antigen retrieval (pH 6.1 citrate buffer; Target Retrieval Solution, Dako, Carpinteria, CA) using a mouse monoclonal antibody directed against SARS-CoV-2 S (clone 1A9, catalog number GTX632604; GeneTex, Irvine, CA), followed by detection using EnVision + (Dako). One positive control was included in each run consisting of placental tissue with strong SARS-CoV-2 immunohistochemical staining in cytotrophoblast and syncytiotrophoblast as well as detection of SARS-CoV-2 RNA by ISH, as previously described[14]. Each slide was evaluated by two pathologists (AS and CPH) for the presence of positive staining in decidua, basal plate, chorionic plate, villous trophoblast, extravillous trophoblast and/or villous stroma. Background, non-specific chromogen deposition was discounted from the interpretation. Clinical and pathologic characteristics were then correlated with immunohistochemical results.

SARS-CoV-2 RNA in situ hybridization

Formalin-fixed, paraffin-embedded tissue from six placentas with a short vaccine-delivery interval were used. We used the RNA-scope2.5 LS Probe-V-nCoV2019-S (catalog number 848568; Advanced Cell Diagnostics, Newark, CA) and the BOND RNAscope Detection Reagents – Brown on an automated Bond III platform (Leica Biosystems, Buffalo Grove, IL). RNA unmarking was done using Bond Epitope Retrieval Solution 2 for 15 min at 95 °C followed by protease treatment for 15 min and probe hybridization for 2 h. Signal was amplified by a series of signal amplification steps followed by brown color development for light microscopy visualization.

RESULTS

A total of 48 subjects met inclusion criteria. Clinical and pathologic characteristics of the vaccinated cohort are presented in Table 1. Average age was 34 years (median 34, range 24–41 years). Most patients (37, 77%) delivered during the third trimester: of these 24 were term (37 weeks or more) and 13 were preterm (27–36 weeks). Two patients (4%) delivered during the second trimester at 23 and 26 weeks. Three patients (6%) underwent elective pregnancy termination during the second trimester, two for fetal trisomy 21 (at 16 and 17 weeks, respectively) and one for fetal complex cardiac anomalies (at 17 weeks). The remaining 6 subjects (10.4%) presented with spontaneous abortion during the first trimester (15 weeks or earlier). A total of 25 subjects (52%) received two doses of mRNA vaccine and the remaining 25 (48%) received one dose during pregnancy (and the second dose after delivery). Seventeen (35%) received the Moderna vaccine, and 31 (65%) the Pfizer vaccine. The interval between the latest vaccine dose and the delivery or pregnancy loss was in average 19 days (median 13, range 2–79 days); in 30 (63%) patients, the interval was 15 weeks or less.

The positive immunohistochemical controls showed robust staining in cytotrophoblast and syncytiotrophoblast. Conversely, all placentas in the study and negative control groups were negative for SARS-CoV-2 S protein staining by immunohistochemistry (Fig. 1). Cases 10, 18, 19, 24, 28, and 30 were tested for SARS-CoV-2 RNA by ISH. These cases had an interval between placental delivery and vaccination ranging from 2 to 7 days (median 4 days, Table 1). All six placental tissues were negative for in situ hybridization testing (Fig. 1).

DISCUSSION

Our study shows absence of the SARS-CoV-2 Spike protein in the placenta of patients with history of mRNA vaccination. None of the placentas examined showed the strong cytoplasmic immunohistochemical staining in villous trophoblast, endothelium, or villous stroma that is expected in cases with active Spike protein translation. Although this may be due to a long interval between vaccination and placental evaluation, negative immunohistochemical staining was also seen in patients vaccinated within 14 days prior to delivery. Moreover, in situ hybridization was negative in six cases with some of the shortest intervals between delivery and vaccination.

It has been recently shown that vaccinated patients against SARS-CoV-2 without evidence of active COVID-19 infection at the time of delivery have no increased incidence of decidual arteriopathy, fetal vascular malperfusion, villitis or histiocytic intervillositis compared to patients with no documented vaccination or SARS-CoV-2 infection[15]. Also, as per the American College of Obstetrics and Gynecologist there have been no specific safety signals reported in pregnant individuals enrolled in the v-safe COVID-19 Vaccine Pregnancy Registry, or the Vaccine Adverse Event Reporting System. These findings correlate with the lack of safety concerns in pregnancy during the Developmental and Reproductive Toxicity animal-model studies for the Pfizer-BioNtech and Moderna vaccines[16,17]. Our study shows similar findings with no prevalent pathology in our vaccinated population.

While the effects of COVID-19 during pregnancy remain to be fully elucidated, the current literature indicates an increased risk of fetal complications. The rates of pre-term labor in COVID-19 infected patients during the third trimester range from 15-43%, higher than the national average of 10% previously determined in the gestational population of the United States[5,6]. In addition, intrauterine growth restriction has been documented in 10% of cases, and miscarriage in 2%[6]. Several studies have explored the possibility of placental infection and vertical transmission by SARS-CoV-2. Most have found no detectable SARS-CoV-2 by either RNA in situ hybridization[18] or immunohistochemistry[19]. However, cases with detectable SARS-CoV-2 in the placenta have been documented[7,14,20]. Placentas with SARS-CoV-2 positivity (by

Table 1. Clinical and pathologic characteristics of patients with mRNA SARS-CoV-2 vaccination during pregnancy.

Case	Patient age	Type	# of doses during pregnancy	Vaccine to delivery interval (days)	Gestational Age (weeks)	Co-morbidities	Placental weight (grams)	Placental weight percentile
19	41	Pfizer	1	2	39	Advanced maternal age	710	>90%
24	30	Pfizer	2	2	40	Post partum hemorrhage	630	>90%
29	37	Pfizer	1	4	34	None	1071	>90%
25	34	Moderna	2	4	37	Intrauterine growth restriction	385	<10%
27	41	Pfizer	1	4	37	None	668	10–25%
26	34	Moderna	2	4	38	Pregnancy induced hypertension	448	10–25%
28	30	Pfizer	2	4	39	None	507	25–50%
8	41	Pfizer	1	5	32	Placenta previa, advanced maternal age	378	50–75%
30	31	Pfizer	1	5	38	Cholestasis of pregnancy	590	75–90%
31	36	Pfizer	2	5	40	None	470	10–25%
32	37	Moderna	1	6	36	Premature rupture of membranes	366	<10%
18	31	Pfizer	1	6	39	Graves disease	565	50–75%
33	30	Pfizer	2	6	39	Intrauterine growth restriction in prior pregnancy	402	10–25%
10	33	Moderna	2	7	36	Intrauterine growth restriction	358	<10%
34	30	Pfizer	1	8	6	None	N/A	Fragmented
35	34	Pfizer	1	8	39	None	793	>90%
36	38	Pfizer	1	9	9	None	N/A	Fragmented
37	31	Pfizer	1	10	26	HELLP syndrome	134	<10%
38	37	Pfizer	1	10	36	Preeclampsia with severe features	400	10–25%
39	34	Pfizer	1	10	39	Small for gestational age	423	<10%
21	32	Pfizer	2	10	40	None	557	50–75%
40	34	Moderna	1	11	33	Premature rupture of membranes	449	<10%
4	40	Pfizer	1	13	16	None	N/A	N/A
6	33	Moderna	2	13	17	None	N/A	N/A
41	30	Pfizer	2	13	36	Fetal lower urinary tract obstruction	409	10–25%
42	34	Pfizer	1	13	39	In vitro fertilization	546	50–75%
43	32	Pfizer	1	13	40	Decreased fetal movement	520	25–50%
44	37	Pfizer	1	14	34	None	455	50–75%
17	35	Pfizer	1	14	39	Type II diabetes	529	50–75%
45	40	Pfizer	1	15	13	None	N/A	Fragmented
1	38	Moderna	1	16	8	None	N/A	N/A
15	35	Moderna	2	16	38	History of placenta accreta	361	<10%
46	29	Pfizer	1	18	23		104	<10%

Table 1. continued

Case	Patient age	Type	# of doses during pregnancy	Vaccine to delivery interval (days)	Gestational Age (weeks)	Co-morbidities	Placental weight (grams)	Placental weight percentile
						Premature rupture of membranes		
47	35	Pfizer	2	20	38	Pregnancy-induced hypertension	637	>90%
48	38	Pfizer	1	21	36	None	454	50–75%
5	34	Moderna	1	23	17	None	N/A	N/A
14	35	Moderna	2	25	37	Intrauterine growth restriction	291	<10%
11	24	Moderna	2	32	36	Preeclampsia with severe features	540	75–90%
13	32	Moderna	2	34	37	Gestational diabetes	424	10–25%
9	32	Pfizer	2	38	35	Preeclampsia with severe features	421	25–50%
22	33	Moderna	2	38	40	None	560	50–75%
16	39	Moderna	2	39	38	None	477	25–50%
12	31	Pfizer	2	45	36	Preeclampsia with severe features	424	25–50%
3	35	Moderna	2	46	9	None	N/A	N/A
7	38	Moderna	2	51	30	Pre-term labor	202	<10%
20	39	Moderna	2	65	39	None	586	75–90%
2	36	Pfizer	2	68	9	None	N/A	N/A
23	25	Pfizer	2	79	41	Non-reassuring fetal heart rate	514	25–50%

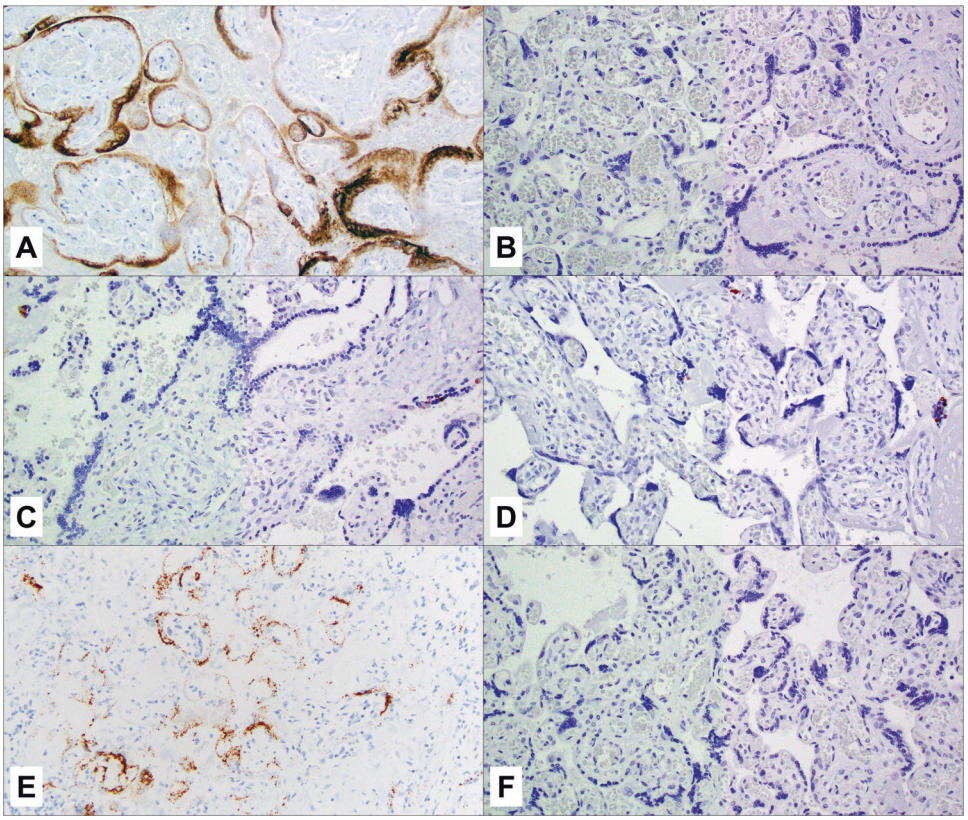

Fig. 1 SARS-CoV-2 Spike protein detection. A Immunohistochemistry shows robust, strong and diffuse positivity in villous trophoblast in the placenta of a patient with positive in situ hybridization for SARS-CoV-2 which was used as positive control. **B**, **C** In contrast, immunohistochemical staining was negative in placentas from patients with history of mRNA vaccination. **D** Stain was also negative in third-trimester placentas collected in 2018, which served as negative controls. The positive control was also used as control for SARS-CoV-2 in situ hybridization; the control shows strong signal in trophoblast (**E**), whereas six placentas in the study group were negative (**F**).

immunohistochemistry, ISH, and RT-PCR) are characterized by trophoblast damage in the form of villous trophoblast necrosis, perivillous fibrin deposition, histiocytic intervillositis and collapse of the intervillous space[20]. Remarkably, these findings are diffuse and severe in cases of intrauterine fetal demise[20]. All the above complications highlight the importance of vaccination against COVID-19 before or during pregnancy.

mRNA vaccines work under the principle of inoculating specific mRNA that can be translated by human cells in vivo to produce specific proteins, in this case the Spike protein of SARS-CoV-2 (or components of it like the receptor-binding domain) that elicit a specific humoral and cellular immune response. An additional advantage of mRNA vaccines is the use of lipid nanoparticles which not only protect mRNA from degradation after inoculation, but also contain surface molecules with affinity for leukocyte subsets such as macrophages, monocytes, dendritic cells and lymphocytes, allowing for cell-specific delivery[21,22]. Protein production via mRNA translation is not only cell-specific but also largely confined to the site of injection when administration is subcutaneous, intradermal or intramuscular, although the latter approach could result in transit of mRNA lipid nanoparticles and active translation in peripheral sites like the liver[23]. Antigen-presenting leukocytes return to the circulation and elicit secondary immune responses in the spleen and other lymphoid organs. In the setting of pregnancy, it is conceivable that maternal leukocytes containing vaccine SARS-CoV-2 mRNA reach the placenta. Nonetheless, active translation does not appear to occur in this organ based on our results.

A range of placental histopathologic findings has been reported in patients infected with COVID-19 during pregnancy including inflammatory processes (chronic villitis, chronic deciduitis, features of ascending intrauterine infection), maternal vascular malperfusion (placental infarction, accelerated villous maturation, decidual arteriopathy) and fetal vascular malperfusion (fetal vascular thrombosis)[19,24,25]. Nonetheless, the incidence of such findings is not significantly different than in patients without SARS-CoV-2 infection[19].

Future investigations should focus on validating our findings and, ideally, test for Spike protein accumulation or presence of mRNA in the placenta under controlled conditions. Whether SARS-CoV-2 mRNA vaccine components reach the placenta and undergo translation within the first 48 h after inoculation remains to be determined, as we were unable to control for the vaccination-delivery interval and the shortest interval observed in our series was 2 days. Whether mRNA vaccine components reach the fetus while sparing the placenta also cannot be excluded based on our study design.

This study includes a well-characterized cohort of pregnant subjects, and testing followed validated protocols for SARS-CoV-2 Spike glycoprotein (protein expression by immunohistochemistry and mRNA by in situ hybridization). Nonetheless, we acknowledge that many of the variables of interest could not be controlled. For instance, the vaccination-delivery interval varied among patients. Animal studies suggest that mRNA vaccine-encoded antigens can be detected in regional lymph nodes and/or tissues up to 10 days post-vaccination, and occasionally in the liver for up to 1–4 days[1,23]. To minimize the likelihood of false negatives due to long vaccination-delivery intervals, we enriched our cohort with placenta from patients with short intervals (22 cases had vaccination to delivery intervals of 10 days or less). An additional limitation pertains to the unavailability of a positive control expressing the spike protein encoded by the vaccine mRNA. Ideally, future control studies validating our findings should include a positive control from human tissue of a non-infected patient expressing the spike protein

encoded by the vaccine mRNA. We believe our results are still valid for two main reasons: First, we utilized two different methodologies: in situ hybridization to directly detect the vaccine mRNA, as well as immunohistochemistry to detect the mRNA translation product (spike protein). Second, the mRNA vaccines assessed in this study are known to encode the full-length SARS-CoV-2 spike protein. The mRNA sequence in the vaccine is identical to that of the native virus, except for two stabilizing mutations in amino acids K986P and V987P[1,26]. Both our monoclonal immunohistochemical antibody and the RNAScope probes target an epitope and an RNA sequence outside of these two mutations as per manufacturers datasheets, respectively. Specifically, our antibody targets an epitope in the amino acids 1029-1192 of the SARS-CoV-2 spike protein, and our RNAScope probes target the RNA sequence encoding amino acids 22 and 580. Both areas are unmodified in mRNA vaccines, and therefore any accumulation of S protein or RNA in placental tissues would be detected by our methods of choice.

In summary, immunization with mRNA vaccines against SARS-CoV-2 does not lead to translation or accumulation of the Spike protein in the placenta, as detected by in situ hybridization and immunohistochemistry. This observation is in keeping with the cell and tissue-specific delivery characteristic of mRNA vaccine technologies. It also provides further evidence underscoring the safety of mRNA vaccines during pregnancy.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

AS, MAS, and CPH designed the study, collected and analyzed the data, and drafted the manuscript. JLH and BJQ contributed with acquisition and analysis of immunohistochemical data. AJN, IHS and DJR contributed with acquisition and analysis of in situ hybridization data. All authors read, edited and approved the final version of the manuscript.

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ETHICS APPROVAL/CONSENT TO PARTICIPATE

This project was approved by the Brigham and Women's Hospital Institutional Research Board (Protocol # 2021P001022). Prospective consent collection was waived.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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