Research Letter

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Pregnancy

Measures of Immunity and Placental Histopathology

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INTRODUCTION

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been approved for emergency use, but, despite elevated risk of severe disease, pregnant women were excluded from the clinical trials that led to their authorization.[1] Placental findings can indicate potential clinical risk and could be an early signal for rare injury seen only after widespread use in the pregnant population.[2–6]

Maternal SARS-CoV-2 infection has been associated with decidual arteriopathy, fetal vascular malperfusion, and chronic histiocytic intervillositis.[7–9] mRNA vaccines induce an immune response through activation of TLR3, which has been linked to decidual arteriopathy, growth restriction, preterm delivery, and fetal loss in mouse models.[10–14]

Our objective was to evaluate the frequency of these key placental lesions in patients who received SARS-CoV-2 vaccination in pregnancy.

METHODS

The study methods have been described previously and were approved by the Northwestern University institutional review board.[7,15] We report results from patients who tested negative for SARS-CoV-2 infection on polymerase chain reaction who received vaccine (delivering between January and April 2021) and unvaccinated women in a control group (negative for SARS-CoV-2 infection on polymerase chain reaction, immunoglobulin G– and immunoglobulin M–negative, delivering between April 2020 and April 2021) from an ongoing coronavirus disease 2019 (COVID-19) cohort study. Antibody testing used the ACCESS SARS-CoV-2 spike protein RBD test.

Statistical testing was performed with unpaired *t* tests or Fisher exact test for demographics and logistic regression with gestational age as a covariate for placental lesions (Python SciPy 1.6.1). A post hoc power calculation was performed, demonstrating at least 80% power to identify a 2.5-fold or higher increased risk of any lesion with a baseline prevalence of 10% or greater and a threefold or higher increased risk of any lesion with a baseline prevalence of 7% or greater (Stata 15.0).

RESULTS

We report findings in 84 women who received a SARS-CoV-2 vaccine during pregnancy and 116 women in a control group who did not receive a vaccine (Table 1). Women with vaccination were more likely to deliver vaginally. The first inoculation was 46±24 days before delivery for the 75 patients with known vaccination timing. Vaccinated women showed robust antibody responses, whereas women in the control group were negative (Fig. 1 and Table 1).

Placental examination in women with vaccination showed no increased incidence of decidual arteriopathy, fetal vascular malperfusion, low-grade chronic villitis, or chronic histiocytic intervillositis compared

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Table 1. Clinical, Immunologic, and Histologic Findings

	Vaccine Group (n=84)	Control Group (n=116)	aOR (95% CI)*	*P*
Clinical characteristics				
Maternal age (y)	33.7±3.1	32.5±4.8		.07
1st vaccine-to-delivery interval (d) (n=75)	45.9±24.3	NA		
Gestational age at delivery (wk)	38.5±2.4	38.4±1.9		.86
Vaginal delivery	66 (79%)	75(65%)		.04
Anti–SARS-CoV-2 signal/cutoff ratio (n=52 vaccine group, 116 control group)				
IgG	22.8±14.5	0.04±0.05		<.001
IgM	4.1±13.2	0.19±0.12		.001
Placental findings				
Decidual arteriopathy	8 (10)	14 (12)	0.75 (0.3–1.9)	.55
Fetal vascular malperfusion	5 (6)	8 (7)	0.85 (0.27–2.7)	.78
Low-grade chronic villitis	10 (12)	9 (8)	1.6 (0.62–4.2)	.33
High-grade chronic villitis	4 (5)	16 (14)	0.31 (0.1–0.97)	.04
Chronic histiocytic intervillositis†	0 (0)	2 (1.7)	—	—

aOR, adjusted odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ig, immunoglobulin.
Data are mean±SD or n (%) unless otherwise specified.
* Adjusted for gestational age at delivery.
† Multivariate modeling cannot be performed for chronic histiocytic intervillositis given the low incidence.

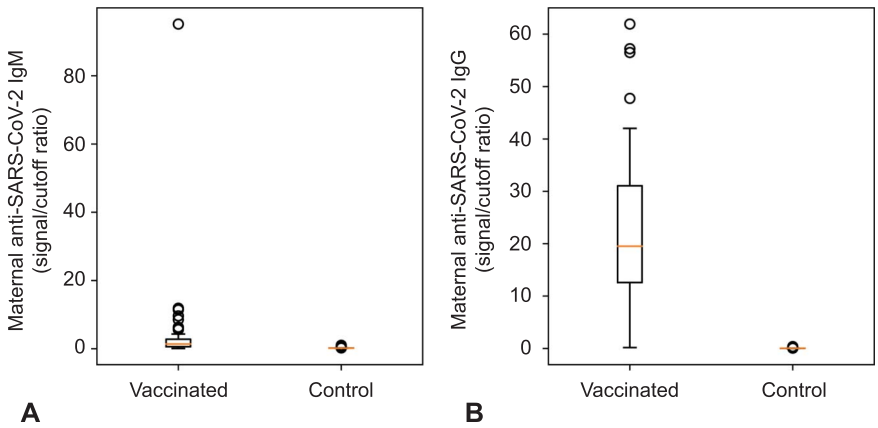

Fig. 1. Maternal anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein immunoglobulin (Ig)M (**A**) and IgG (**B**) at delivery. Vaccinated patients showed frequent (30/52 over cutoff) IgM and robust (50/52) IgG; women in the control group did not (0/116 and 0/116).

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with women in the control group (Table 1). Incidence of high-grade chronic villitis was higher in the control group than in the vaccinated group.

DISCUSSION

In our cohort of vaccinated pregnant patients, there was no observed increase in the incidence of findings characteristic of SARS-CoV-2 infection in pregnancy and no evidence of vaccine-triggered breakdown in maternal immunologic tolerance of the fetus.[16] Although limited by population differences between vaccinated and unvaccinated patients,[17,18] these findings add to the growing literature supporting the safety of SARS-CoV-2 vaccination in pregnancy.

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