

# 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.<sup>1</sup> 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.<sup>2–6</sup>

Maternal SARS-CoV-2 infection has been associated with decidual arteriopathy, fetal vascular malperfusion, and chronic histiocytic intervillitis.<sup>7–9</sup> 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.<sup>10–14</sup>

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 Univer-

sity institutional review board.<sup>7,15</sup> 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  $46 \pm 24$  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 intervillitis compared

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### Financial Disclosure

*The authors did not report any potential conflicts of interest.*

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**Table 1. Clinical, Immunologic, and Histologic Findings**

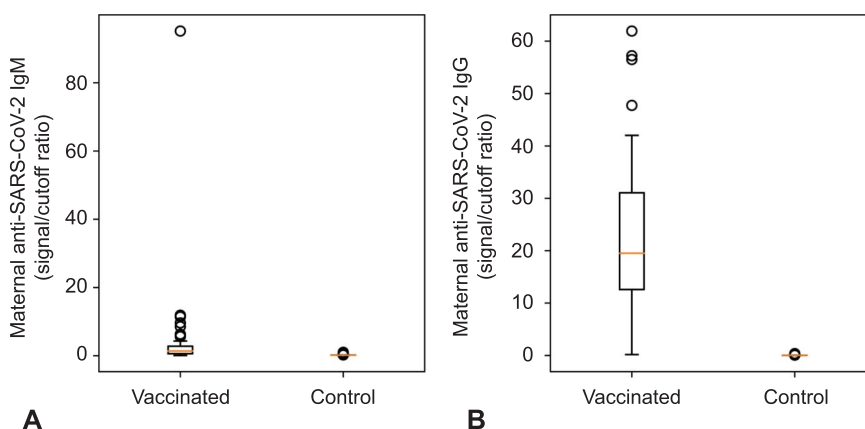
	Vaccine Group (n=84)	Control Group (n=116)	aOR (95% CI)*	P
Clinical characteristics				
Maternal age (y)	33.7±3.1	32.5±4.8		.07
1st vaccine-to-delivery interval (d) (n=75)	45.9±24.3	NA		
Gestational age at delivery (wk)	38.5±2.4	38.4±1.9		.86
Vaginal delivery	66 (79%)	75(65%)		.04
Anti-SARS-CoV-2 signal/cutoff 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 intervillitis <sup>†</sup>	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.

<sup>†</sup> Multivariate modeling cannot be performed for chronic histiocytic intervillitis 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.<sup>16</sup> Although limited by population differences between vaccinated and unvaccinated patients,<sup>17,18</sup> these findings add to the growing literature supporting the safety of SARS-CoV-2 vaccination in pregnancy.

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