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Placental pathology in women vaccinated and unvaccinated against SARS-CoV-2

OBJECTIVE: SARS-CoV-2 infection during pregnancy has been shown to increase the risk of severe outcomes with pathologic sequelae in the placenta.[1,2] Vaccination against SARS-CoV-2 in pregnant women has been shown to be safe and effective at preventing COVID-19 infection during pregnancy[3,4] and offers protection in the form of antibodies to neonates. This study examined the effects of SARS-CoV-2 messenger RNA (mRNA) vaccination on placental pathology, birthweight, and Apgar score.

STUDY DESIGN: A convenience sample of 431 placentas from women who gave birth to a living singleton between April 18, 2020 and July 31, 2021 at a single New York City hospital and had no history of positive reverse transcription polymerase chain reaction testing, was included in this study. Unvaccinated women who did not receive any SARS-CoV-2 vaccine dose before delivery and who were anti-S negative were included. Fully vaccinated women who received at least 2 doses of a SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech, Collegeville, PA; or ModernaTX, Cambridge, MA) at >2 weeks before delivery, were included if they did not have positive anti-N antibodies that are produced in the setting of infection. Anyone with incomplete vaccine administration was excluded.

The placentas and neonatal outcomes from 164 fully vaccinated women were compared with those of 267 unvaccinated women. The placentas were grossed and microscopically reviewed as previously described.[2] The timing and types

TABLE
Demographics and placental and neonatal findings from patients vaccinated and unvaccinated against SARS-CoV-2

Clinical variable	Total n = 431	Unvaccinated n = 267	Vaccinated n = 164	*P* value
Maternal age (mean)	35.5 (4.7)	35.1 (4.9)	36.2 (4.4)	—
Gestational age (median)	39.0 (1.9)	39.0 (1.9)	39.0 (1.7)	—
Mode of delivery				
Cesarean delivery	194 (45%)	118 (44.2%)	76 (46.3%)	—
Vaginal delivery	237 (55%)	149 (55.8%)	88 (53.7%)	—
Preterm birth (<37 wk)	58 (13.4%)	43 (16.1%)	15 (9.1%)	.056
Low placental weight[a]	86 (20%)	55 (20.6%)	31 (18.9%)	.747
Apgar score 1 min				.271
6	8 (1.9%)	7 (2.6%)	1 (0.6%)	—
7	23 (5.3%)	17 (6.4%)	6 (3.7%)	—
8	84 (19.5%)	42 (15.7%)	42 (25.6%)	—
9	290 (67.3%)	182 (68.2%)	108 (65.9%)	—
Apgar score 5 min				.783
6	6 (1.4%)	4 (1.5%)	2 (1.2%)	—
7	5 (1.2%)	4 (1.5%)	1 (0.6%)	—
8	27 (6.3%)	19 (7.1%)	8 (4.9%)	—
9	383 (88.9%)	231 (86.5%)	152 (92.7%)	—
Small for gestational age birthweight[b]	61 (14.2%)	35 (13.1%)	26 (15.9%)	.556

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TABLE
Demographics and placental and neonatal findings from patients vaccinated and unvaccinated against SARS-CoV-2 *(continued)*

Clinical variable	Total n = 431	Unvaccinated n = 267	Vaccinated n = 164	*P* value
Fetal vascular malperfusion				
Thrombosis of fetal vessels	32 (7.4%)	18 (6.7%)	14 (8.5%)	.616
Intramural fibrin deposition	29 (6.7%)	18 (6.7%)	11 (6.7%)	1
Avascular villi	41 (9.5%)	24 (9%)	17 (10.4%)	.761
Villous stromal karyorrhexis	6 (1.4%)	4 (1.5%)	2 (1.2%)	1
Maternal vascular malperfusion				
Villous infarct	71 (16.5%)	45 (16.9%)	26 (15.9%)	.89
Retroplacental hemorrhage	5 (1.2%)	5 (1.9%)	0 (0%)	.194
Accelerated villous maturation	38 (8.8%)	29 (10.9%)	9 (5.5%)	.083
Increased syncytial knots	46 (10.7%)	30 (11.2%)	16 (9.8%)	.747
Decidual vasculopathy	17 (3.9%)	14 (5.2%)	3 (1.8%)	.13
Villous agglutination	9 (2.1%)	5 (1.9%)	4 (2.4%)	.958
Increased perivillous fibrin	27 (6.3%)	14 (5.2%)	13 (7.9%)	.362
Distal villous hypoplasia	1 (0.2%)	0 (0%)	1 (0.6%)	.805
Delayed villous maturation	23 (5.3%)	16 (6%)	7 (4.3%)	.581
Intervillous thrombus	70 (16.2%)	42 (15.7%)	28 (17.1%)	.816
Chronic histiocytic intervillositis	2 (0.5%)	0 (0%)	2 (1.2%)	.281
Eosinophilic T-cell vasculitis	2 (0.5%)	2 (0.7%)	0 (0%)	.703
Chronic villitis	74 (17.2%)	44 (16.5%)	30 (18.3%)	.724
Chorangiosis	16 (3.7%)	11 (4.1%)	5 (3%)	.758
Vaccine type				
Pfizer	—	—	130 (79.3%)	—
Moderna	—	—	34 (20.7%)	—
Gestational age at vaccination (median)				
Dose 1	25.7	—	25.7	—
Dose 2	29	—	29	—
Detectable cord blood antibodies	—	—	156 (95.1%)	—

[a] Low placental weight: <10th percentile for gestational age; [b] Small for gestational age birthweight: <10th percentile for gestational age using Fenton curves.

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of vaccination, neonatal weights, and Apgar scores were retrospectively abstracted from clinical charts. We studied the incidence of pathologic findings across grouped placentas using the chi-square test of independence for all categorical variables. The continuous variables were compared using the Kruskal–Wallis rank sum test or the Wilcoxon rank sum test.

Statistical analyses were performed using R 3.6.3 (RStudio 1.1.463; RStudio Team, Boston, MA).

This study was approved by the institutional review board at Weill Cornell Medicine.

RESULTS: The vaccinated and unvaccinated groups had similar demographics, including maternal age, gestational age at birth, and mode of delivery (Table).

Among the 164 vaccinated women, the average gestational age for receiving dose 1 was 25.7 weeks and that for dose 2 was 29 weeks. Overall 130 women received the Pfizer vaccine, and 34 received the Moderna vaccine.

There was no significant difference in the placental findings, birthweight, or Apgar scores between the vaccinated and unvaccinated groups (Table). 28 of 164 (17.1%) women from the

vaccinated group and 70 of 267 (26.2%) women from the unvaccinated group had a comorbidity of preeclampsia, hypertension, or intrauterine growth restriction, and a subanalysis excluding those cases did not alter the findings (data not shown).

A total of 95.1% (100% of all tested) neonates born to vaccinated mothers had detectable anti-S immunoglobulin G in the umbilical cord blood, which was similar to previous findings.[5]

CONCLUSION: This secondary analysis builds on the existing body of knowledge demonstrating that SARS-CoV-2 vaccines are safe during pregnancy. Unlike previous studies that have primarily focused on pregnancy and neonatal outcomes, here we specifically examined placental pathology. There was no significant difference in placental findings between the vaccinated and unvaccinated groups, further emphasizing the safety of vaccination during pregnancy. ■

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Reconsidering absolute diagnostic thresholds in intrahepatic cholestasis of pregnancy

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OBJECTIVE: Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and elevated serum bile acid levels after 20 weeks' gestation, and it is associated with adverse perinatal outcomes such as fetal demise, preterm birth, and neonatal respiratory distress syndrome. Determining total bile acid levels is critical for ICP diagnosis and management, and current guidelines use an absolute threshold of 10 μmol/L for diagnosis and thresholds of 40 and 100 μmol/L for disease severity.[1] However, the normal reference range for total bile acid level varies depending on assay methodology,[2] limiting the utility of absolute diagnostic thresholds in diagnosing and treating ICP. We sought to evaluate variation in total bile acid assays by laboratory, testing method, and fasting state.

STUDY DESIGN: We compiled a list of laboratories offering total bile acid measurement within North America, the United Kingdom, and Australia. Bile acid test type, reference range, and fasting requirements were obtained via laboratory websites or by phone. Reference ranges were compared with ICP diagnostic (10 μmol/L) and severity thresholds (40 or 100 μmol/L).

RESULTS: We identified 7 laboratories with total bile acid assays located in the United States (4), Canada (1), United Kingdom (1), and Australia (1) (Table). Four laboratories also offered a fractionated assay (ARUP, Salt Lake City, Utah; Labcorp, Dublin, Ohio; Quest Diagnostics, San Juan Capistrano, California; and Northwell, Calabasas Hills, California). Depending on the test used, the upper limit of normal for total bile acids ranged from 6.8 to 19.0 μmol/L, with lower thresholds for fractioned assays (6.8–9.2 μmol/L) than for unfractionated assays (10–19 μmol/L). Only 1 laboratory provided a pregnancy-specific range (≤8.3 μmol/L; Quest). Bile acids were measured using high-performance liquid chromatography, gas chromatography with mass spectrometry, or through quantitative enzymatic methods using spectrophotometry. Fasting was preferred or required in 10 of 11 assays, either overnight (n=2), for 8 hours (n=4), or for an unspecified duration (n=4). Using ICP severity