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The Protective Effect of Maternal COVID-19 Vaccination Against Adverse Obstetric-Perinatal Outcomes and Placental Malperfusion

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ABSTRACT

Background: SARS-CoV-2 infection during pregnancy is associated with significantly increased risks of severe clinical complications and adverse perinatal outcomes. While vaccination is established as a safe preventive measure, its specific impact on pathophysiological drivers, such as systemic coagulopathy and placental vascular integrity, remains insufficiently explored in local clinical settings.

Objectives: This study evaluates the independent protective role of SARS-CoV-2 vaccination against infection severity, coagulation abnormalities, and placental vascular pathology in a Georgian cohort.

Methods: A retrospective, multicenter cohort study of 300 pregnant women with COVID-19 (160 vaccinated, 140 unvaccinated) was conducted between August and October 2021. Multivariable logistic regression, adjusted for maternal age, BMI, and comorbidities, was used to estimate risk. A blinded histomorphological analysis of 60 placentas was performed according to the Amsterdam International Consensus criteria.

Results: The incidence of severe COVID-19 was significantly lower in vaccinated women (5.0% vs. 15.7%; P<0.001). Unvaccinated status was a key risk factor for severe disease (aOR 3.80; 95% CI: 1.90-7.60). Vaccination significantly reduced the rates of Cesarean sections (28.1% vs. 42.9%; P=0.003) and preterm birth. Mechanistically, vaccinated women had significantly lower D-dimer levels (1850±520 ng/mL FEU vs. 2900±780 ng/mL FEU; P<0.001) and a lower incidence of Maternal Vascular Malperfusion (MVM) (33.3% vs. 70.0%; P=0.003).

Conclusions: Vaccination provides a significant protective association with improved clinical stability. By maintaining clinical stability and potentially reducing the risk of placental MVM, vaccination serves as an important physiological buffer, improving obstetric outcomes.

Keywords: COVID-19; maternal vaccination; neonatal outcomes; placental malperfusion; pregnancy; SARS-CoV-2.

BACKGROUND

While mRNA and other COVID-19 vaccines have been established as effective and safe for pregnant patients,[1-3,6] additional studies are needed to investigate the effect of vaccination not only on clinical outcomes but also on specific pathophysiological mechanisms, such as coagulopathy[4] and placental malperfusion[5] - a key driver of poor fetal outcomes. This study aims to evaluate the independent protective effect of COVID-19 vaccination against severe disease progression, coagulation abnormalities, and adverse obstetric-perinatal outcomes in a Georgian cohort.

METHODS

Study design and participants

This was a retrospective, multicenter cohort study conducted in Georgia between August 2, 2021, and October 26, 2021. During this specific study period, the Delta variant of SARS-CoV-2 was the predominant circulating strain in Georgia. The study involved 300 pregnant women with laboratory-confirmed SARS-CoV-2 infection (via RT-PCR). Participants were selected using consecutive sampling to minimize selection bias. Institutional Review Board (IRB) approval was obtained from the Biomedical Research Ethics Committee of Tbilisi State Medical University (Protocol No. 4-2022/97), and the study adhered to the Declaration of Helsinki.

Vaccination status

Participants were categorized into two groups:

(i) The fully vaccinated cohort (n=160) consisted of individuals who received exactly two doses of the mRNA (Pfizer-BioNTech) vaccine, administered with a standard 3- to 4-week (21–28 days) interval, without any booster doses. In this vaccinated group, the median time elapsed from receiving the second vaccine dose to the onset of SARS-CoV-2 infection was 12 weeks.

(ii) The unvaccinated cohort (n=140) included pregnant women who had not received any COVID-19 vaccine.

Clinical and diagnostic definitions

To ensure reproducibility, clinical outcomes were strictly defined:

- "Severe COVID-19" was classified according to WHO guidelines, characterized by oxygen saturation <90% on room air or signs of severe respiratory distress.
- "Neonatal infection" was confirmed via a positive RT-PCR test within the first 24-48 hours of life.
- "Fetal growth restriction" (FGR) was defined as an estimated fetal weight below the 10th percentile for gestational age.
- "Preeclampsia/Eclampsia" was diagnosed based on new-onset hypertension (≥140/90 mmHg) and proteinuria after 20 weeks of gestation.
- A "Low APGAR-Score" was defined as a score of <7 at 5 minutes of life.

Data collection and outcomes

The primary outcome was the incidence of severe COVID-19. Secondary outcomes included obstetric complications (preterm birth, preeclampsia), neonatal outcomes (fetal growth restriction [FGR]), and placental histopathology. A subset analysis was performed on 60 placentas (n=30 per group) according to the Amsterdam International Consensus criteria. These 60 placentas were selected from available tissues in both cohorts using a random sampling approach. Furthermore, we verified that the baseline demographic and clinical characteristics of this 60-patient placental subset did not differ significantly from those of the full cohort (P>0.05), thereby minimizing potential selection bias. To minimize information bias, placental histomorphological analysis was performed by pathologists blinded to both vaccination status and patient clinical severity.

Statistical analysis

Data were analyzed using IBM SPSS Statistics (Version 28.0). Descriptive statistics were used to summarize baseline characteristics. Continuous variables (e.g., maternal age) were compared using Student's t-tests. In contrast, categorical variables (e.g., COVID-19 severity, delivery method, and placental morphology) were assessed using Pearson's $\chi 2$ test or Fisher's exact test, as appropriate. Multivariable logistic regression models were constructed to evaluate the independent protective effect of vaccination. These models were adjusted for potential confounders, including maternal age, BMI, gestational trimester, and chronic comorbidities. Results are reported as adjusted Odds ratios (aOR) with 95% Confidence Intervals (CI). For all analyses, a two-tailed P<0.05 was considered statistically significant. Missing data were handled using a complete-case analysis, as the proportion of missing values was less than 5% across all key variables. Throughout the results, unadjusted group differences (crude rates) are systematically distinguished from multivariable-adjusted odds ratios (aOR).

RESULTS

Baseline characteristics and COVID-19 severity

A total of 300 pregnant women were included in the study (160 vaccinated, 140 unvaccinated). Baseline demographic characteristics, including maternal age (28.5±4.2 vs. 29.1±3.9 years), were comparable between the two groups. The incidence of severe COVID-19 was markedly lower in the vaccinated group (5.0%) than in the unvaccinated group (15.7%; P<0.001). Multivariable logistic regression analysis confirmed that unvaccinated status was a significant independent risk factor for developing severe disease (aOR 3.80; 95% CI: 1.90-7.60), after controlling for maternal age, BMI, and chronic comorbidities (Tab.1)

TABLE 1. Baseline demographic characteristics

Characteristic	Vaccinated (N=160)	Unvaccinated (N=140)	P-value
Maternal age, years (Mean±SD)	28.5±4.2	29.1±3.9	0.230
BMI, kg/m² (Mean±SD)	**26.4 ± 3.2**	**27.1 ± 3.5**	0.180
Normal weight, n (%)	69 (43.1%)	56 (40.0%)	0.210
Overweight, n (%)	43 (26.9%)	64 (45.7%)	0.065
Obese, n (%)	48 (30.0%)	20 (14.3%)	0.090
Trimester at diagnosis, n (%)			0.450
First/Second trimester, n (%)	80 (50.0%)	77 (55.0%)	-
Third trimester, n (%)	80 (50.0%)	63 (45.0%)	-
COVID-19 severity, n (%)			<0.001
Mild	120 (75.0%)	75 (53.6%)	Ref
Moderate	32 (20.0%)	43 (30.7%)	0.038
Severe	8 (5.0%)	22 (15.7%)	<0.001

Abbreviations: aOR, Adjusted Odds ratio; Ref, Reference group; SD, Standard deviation.

Note: Adjusted OR for severe disease was 3.80 (95% CI:1.90-7.60) for the unvaccinated group, controlled for maternal age, BMI, and chronic comorbidities.

Obstetric outcomes

Maternal vaccination was associated with a significant reduction in adverse obstetric outcomes (Tab.2). Preterm birth (<37 weeks) occurred in 7.5% of vaccinated women compared to 17.9% of unvaccinated women (aOR 0.38; 95% CI:0.17-0.86; P=0.006). Preeclampsia rates were also significantly lower in the vaccinated cohort (3.1% vs. 10.7%; aOR 0.27; 95% CI:0.09-0.81; P=0.012). Furthermore, the rate of Cesarean sections was substantially reduced (28.1% vs. 42.9%; P=0.003).

TABLE 2. Adverse obstetric outcomes and associated risks

Obstetric Outcome	Vaccinated (N=160), n (%)	Unvaccinated (N=140), n (%)	*P* value	Adjusted *OR* (95% *CI*)
Preterm birth (<37 weeks)	12 (7.5%)	25 (17.9%)	0.006	0.38 (0.17-0.86)
Preeclampsia/Eclampsia	5 (3.1%)	15 (10.7%)	0.012	0.27 (0.09-0.81)
Fetal growth restriction (FGR)	8 (5.0%)	18 (12.9%)	0.015	0.35 (0.14-0.90)
Delivery method (C-section)	45 (28.1%)	60 (42.9%)	0.003	0.50 (0.30-0.82)
Stillbirth	1 (0.6%)	3 (2.1%)	0.30	0.29 (0.03-2.62)

Abbreviations: CI, Confidence interval; OR, Odds ratio.

Note: Adjusted ORs (with Unvaccinated as Reference) were controlled for maternal age, trimester of infection, and parity.

Neonatal outcomes

Neonatal health indicators showed a protective association with maternal vaccination. There were significantly lower risks for low birth weight (11.9% vs. 26.4%; P<0.001) and low APGAR scores at 5 minutes (6.3% vs. 15.0%; P=0.009) in infants born to vaccinated mothers (Tab.3).

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TABLE 3. Neonatal health outcomes at birth

Criteria	Vaccinated (N=160), n (%)	Unvaccinated (N=140), n (%)	P value	Adjusted OR (95% CI)
Low Birth Weight (<2500g)	19 (11.9%)	37 (26.4%)	< 0.001	0.37 (0.19-0.71)
Neonatal Infection	6 (3.8%)	13 (9.3%)	0.046	0.38 (0.14-0.99)
Low APGAR-Score (<7 at 5 mins)	10 (6.3%)	21 (15.0%)	0.009	0.39 (0.18-0.83)

Abbreviations: CI, Confidence interval; OR, Odds ratio.
Note: Adjusted ORs (with Unvaccinated as the Reference) were controlled for maternal age, severe maternal COVID-19, and gestational age at delivery.

Biomarkers and placental histopathology

Vaccinated women had significantly lower mean D-dimer levels (1850±520 ng/mL FEU) compared to the unvaccinated group (2900±780 ng/mL FEU; P<0.001). Histopathological evaluation of the placental subset (n=60) showed that maternal vascular malperfusion (MVM) was significantly more prevalent in the unvaccinated group (70.0% vs. 33.3%; P=0.003) (Tab.4).

Conversely, normal placental morphology was observed in 66.7% of the vaccinated subset, compared with only 30.0% in the unvaccinated subset (P=0.003).

TABLE 4. Placental histopathology and coagulation biomarkers

Characteristic	Vaccinated	Unvaccinated	P-value
Placental subset (N=60)	**(*n*=30)**	**(*n*=30)**	
Normal morphology	20 (66.7%)	9 (30.0%)	0.003
Maternal vascular malperfusion	10 (33.3%)	21 (70.0%)	0.003
Intervillous fibrin accumulation	10 (33.3%)	17 (56.7%)	0.070
Biomarkers (N=300)	**(*n*=160)**	**(*n*=140)**	
D-dimer (ng/mL FEU) Mean±SD	1850 ± 520	2900 ± 780	< 0. 001
IgG Titer (BAU/mL) Mean± D	4900 ± 1500	450 ± 120	< 0 .001

Abbreviations: BAU, Binding antibody units; FEU, Fibrinogen equivalent units; SD, Standard deviation.
Note: Placental lesions were graded according to the Amsterdam International Consensus criteria. D-dimer levels were measured within 24 hours of hospital admission.

DISCUSSION

Our findings are consistent with the broader national epidemiological landscape in Georgia during 2021 (Supplementary Tab.1) and international systematic reviews regarding the clinical severity of the infection in pregnant populations.[7] The high prevalence of Maternal Vascular Malperfusion (MVM) in our unvaccinated subset (70.0%) reflects an underlying state of vascular vulnerability to the virus.[5,8-10] Vaccination appears to serve as a "physiological buffer," associated with a lower risk of endothelial dysfunction.[11,12] The robust immune response observed - characterized by significantly higher IgG titers - highlights the vaccine's potential to prevent severe placental injury and coagulopathy.[13,14] Maternal SARS-CoV-2 vaccination thus plays a pivotal role in protecting placental health and ensuring favorable neonatal outcomes.[1,2,15-20]

Limitations and external validity

Our study has several limitations that should be acknowledged. Given the retrospective observational nature of our study, the reported associations cannot definitively prove mechanistic causality. Residual confounding remains a possibility, as unmeasured variables - such as socioeconomic status, parity, smoking habits, the exact time elapsed since vaccination, and access to prenatal care - could systematically differ between groups, leading our adjusted odds ratios to reflect residual confounding still. Furthermore, while multivariable models for neonatal outcomes adjusted for maternal COVID-19 severity, we must acknowledge the concept of mediation: the improved obstetric outcomes (such as lower preterm birth and Cesarean rates) and preserved placental morphology may be partially or largely mediated indirectly by the reduced severity of maternal illness, rather than solely by an independent mechanistic effect of the vaccine. Finally, regarding external validity, this cohort represents a specific early-vaccination phase of the pandemic (August-October 2021), during which the Delta variant was dominant. Therefore, these findings may not fully generalize to later SARS-CoV-2 variants, booster-era immunity, or contemporary hybrid immunity scenarios.

CONCLUSIONS

Maternal SARS-CoV-2 vaccination is associated with both maternal clinical stability and placental health. Our findings demonstrate that vaccination is significantly associated with lower rates of systemic coagulopathy and preserved placental vascular integrity, acting as a critical physiological buffer that improves obstetric and neonatal outcomes.

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CONFLICT OF INTEREST

The authors declare that they have no financial or personal relationships with any individuals or organizations that could inappropriately influence or bias the content of this manuscript.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTAL TABLE 1. National epidemiological data of COVID-19 in pregnant and postpartum women in Georgia (January-August 2021)

Category	Value / Summary
Total COVID-19 cases (Pregnant/Postpartum)	10,759
Prevalence among reproductive-age women, %	11
Outpatient management (Home-based), %	73%
Inpatient management (Hospitalized), % (n)	23 (3,464)
Intensive care unit (ICU) admissions, % (n)	0.1 (15)
Total maternal mortality, n	16
Primary cause of death: Pneumonia, n	13
Gestation period at death (29-40 weeks), %	87.5
Post-cesarean section mortality rate, %	85.7
Deaths during pregnancy, n	2
Deaths postpartum (within 42 days), n	14

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