Impact of COVID-19 disease and COVID-19 vaccination on maternal or fetal inflammatory response, placental pathology, and perinatal outcomes

OBJECTIVE: COVID-19, even mild, is associated with a host inflammatory response,[1] which has not been well delineated in pregnancy. COVID-19 is associated with preterm birth,[2] preeclampsia,[2] and placental vascular pathology.[3] Although COVID-19 vaccination does result in mild viral-type symptoms associated with a heightened immune response, it is not known whether this immune response results in inflammatory cytokine pathway activation. Our objective was to evaluate the impact of COVID-19 and COVID-19 vaccination on the maternal-fetal unit through the study of the inflammatory cytokine panel at delivery, placental pathology, and perinatal outcomes.

STUDY DESIGN: This was a retrospective cohort study of pregnant patients who delivered at Thomas Jefferson University Hospital from March 2020 to July 2021 and consented to an ongoing delivery sample biorepository. With our convenience sample of approximately 300, we anticipated a rate of at least 15% of COVID-19 or COVID-19 vaccination or n≥50 in each group. The cohort was categorized as (1) control (no COVID-19 or COVID-19 vaccination history), (2) COVID-19 (confirmed via polymerase chain reaction) during pregnancy, and (3) COVID-19 messenger RNA (mRNA) vaccination during pregnancy (patient report). Those with both COVID-19 and COVID-19 vaccination were excluded. Placental histopathology was sent for standard clinical criteria (Supplemental Box 1). Cytokine paneling was completed on those with maternal or cord blood samples available and without a diagnosis of clinical triple I. Cytokine analysis was performed using the Meso Scale Diagnostics platform using the 10-Plex Human Proinflammatory Panel Kit (interleukin (IL)-1β, IL-8, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-13, interferon gamma, and tumor necrosis factor alpha [TNFα]) and read on a QuickPlex SQ120 (Meso Scale Diagnostics, Gaithersburg, MD).

RESULTS: Overall, 306 participants were included in the study: 198 in the control group, 59 in the group with COVID-19, and 49 in the COVID-19 vaccination group. There were significant differences in age, body mass index, and race among the groups (Supplemental Table 1). Mean latency to delivery was similar between the COVID-19 vaccination group and the group with COVID-19 (89.5±46.6 days vs 71.0±78.6 days, respectively; P=.14), although more in the COVID-vaccination group had a latency of >30 days from delivery compared with the group with COVID-19 (91.7% vs 60.7%; P<.001). Of those with COVID-19, 54 (91.5%) had mild COVID-19, and none had severe COVID-19.

Maternal cytokine analysis included 142 patients in the control group, 58 patients in the group with COVID-19, and 42 in the COVID-19 vaccination group. The COVID-19 vaccination group had lower median TNFα concentrations than the group with COVID-19 or the control group (P=.001), whereas the group with COVID-19 had higher median IL-6 than the control group (P=.04) (Figure A; Supplemental Figure 1). IL-6 and TNFα levels were not correlated with latency from exposure to delivery (greater than or less than 30 days) among those with COVID-19 (Pearson correlation coefficient [r]=0.10 [P=.48] and r=0 [P>.99], respectively) or among those with COVID-19 vaccination (r=0.12 [P=.46] and r=0.14 [P=.40], respectively).

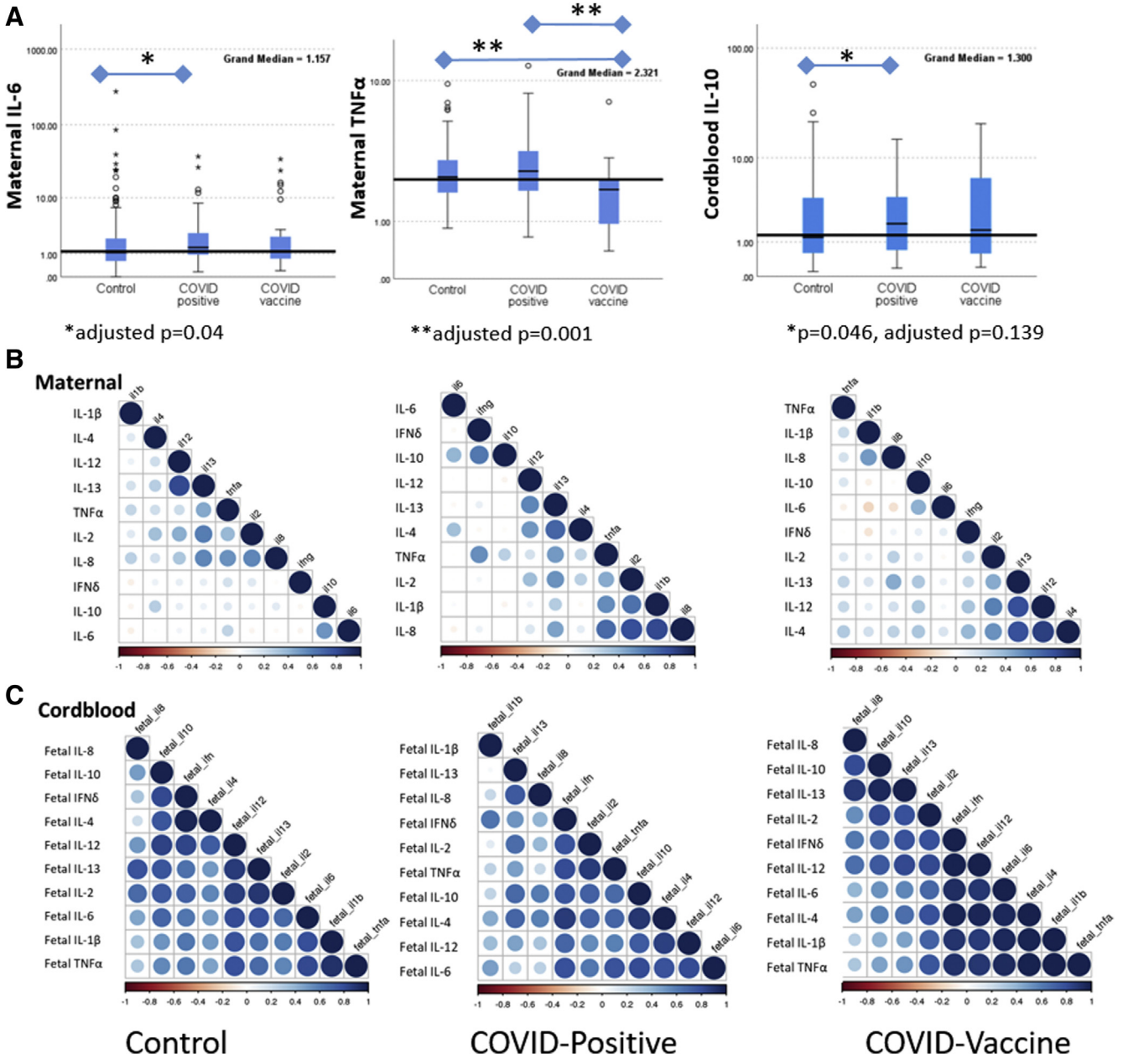
Among cord blood samples, the group with COVID-19, but not the COVID-19 vaccination group, was associated with elevated cord blood IL-10 compared with the control group (P=.04), although this did not remain significant after Bonferroni correction (P=.14) (Figure, A; Supplemental Figure 2).

Correlation matrices were generated to assess differences in the cytokine environment among groups. Significant correlations among IL-12, IL-13, and IL-2 were seen in control maternal samples, and significant correlations among IL-12, IL-13, and IL-4 were seen in COVID-19 vaccination maternal serum samples. These relationships suggest a balanced Th1-to-Th2 profile without a proinflammatory tendency. COVID-19−positive maternal serum samples showed a strong correlation among IL-10, TNFα, IL-1β, and IL-8, indicating a proinflammatory milieu (Figure, B). Cytokine milieu in cord blood samples was similar across cohorts (Figure, C). There was a positive correlation between certain maternal and cord blood Th1 and Th2 markers (IL-12, IL-13, IL-2, IL-4, and TNFα) (Supplemental Figure 3).

Using multivariable logistic regression, we evaluated the association of cytokines with the outcomes of preeclampsia, preterm birth, and placental maternal vascular malperfusion (MVM). No maternal cytokine was associated with preeclampsia or MVM. TNFα was positively associated with preterm birth (β, 1.58 [95% confidence interval (CI), 1.15−2.15; P=.004]) (Supplemental Table 2). Similar findings were noted in the subgroup of those with documented COVID-19 (Supplemental Table 3); TNFα remained

FIGURE

Maternal cytokine analysis of the control group, COVID-19 positive, and COVID-19 vaccine groups



A, Selected cytokines at delivery for control (n=142), COVID-19—positive (n=58), and COVID-19 vaccine (n=42) maternal groups and control (n=140), COVID-19—positive (n=41), and COVID-19 vaccine (n=28) cord blood groups. All cytokine concentrations are in picograms/milliliter. The *P* values listed reflect comparison of medians across groups. *Asterisk* indicates significant difference (Bonferroni correction, adjusted $P<.05$) in pairwise comparison, and *double asterisks* indicate significant difference (Bonferroni correction, adjusted $P<.01$) in pairwise comparison. The full panel of 10 cytokines for maternal and cord blood is available in Supplemental Figures 1 and 2. **B,** Correlation matrices of 10 inflammatory cytokines in maternal blood at delivery for the control (n=140), COVID-19—positive (n=41), and COVID-19 vaccine (n=28) groups. Significant correlations among IL-12, IL-13, and IL-2 were seen in COVID-19—negative, unvaccinated maternal samples, and significant correlations among IL-12, IL-13, IL-4 were seen in COVID-19—negative, vaccinated maternal serum samples. These relationships suggest a balanced Th1-to-Th2 profile without a proinflammatory tendency. Samples from COVID-19—positive maternal serum samples show a strong correlation among IL-10, TNFα, IL-1β, and IL-8, indicating a proinflammatory milieu. **C,** Correlation matrices of 10 inflammatory cytokines in cord blood at delivery for control (n=140), COVID-19—positive (n=41), and COVID-19 vaccine (n=28) groups. Cytokines in cord blood samples were not able to distinguish the different cohorts.

IL, interleukin; *TNFα*, tumor necrosis factor alpha.

Boelig. Impact of COVID-19 and vaccination on the maternal-fetal unit. Am J Obstet Gynecol 2022.

TABLE
Perinatal outcomes

Outcomes	Preterm birth (<37 wk)	Preeclampsia or GHTN	Gestational age at delivery (wk)	Birthweight (g)	Placental MVM
Control (n=198)					
n (%)	13 (6.6)	42 (21.2)	38.9±1.4	3212±513	34 (35.8)
OR (95% CI)	Referent	Referent	Referent	Referent	Referent
aOR (95% CI)	Referent	Referent	Referent	Referent	Referent
COVID-19 positive (n=59)					
n (%)	9 (15.3)	14 (23.7)	38.4±2.2	3131±660	29 (55.8)
OR or MD (95% CI)	2.56 (1.04–6.33) *P*=.04	1.16 (0.58–2.30) *P*=.68	−0.5 (−1.10 to 0.05) *P*=.08	−81 (−267 to 104) *P*=.54	2.26 (1.14–4.50)
aOR or MD (95% CI)	4.54 (1.61–12.78) *P*=.004	1.08 (0.53–2.20) *P*=.84	−0.6 (−1.1 to −0.1) *P*=.01	−122 (−282 to 38) *P*=.13	2.34 (1.16–4.73) *P*=.02
COVID-19 vaccine (n=49)					
n (%)	5 (10.2)	10 (20.4)	38.7±1.8	3255±567	6 (21.4)
OR (95% CI)	1.62 (0.55–4.77), *P*=.38	0.95 (0.44–2.07) *P*=.90	−0.2 (−0.8 to 0.4) *P*=.63	43 (−156 to 244) *P*=.86	0.49 (0.18–1.32)
aOR (95% CI)	1.75 (0.46–6.67) *P*=.41	1.05 (0.45–2.41) *P*=.92	−0.2 (−0.8 to 0.3) *P*=.45	54 (−127 to 236) *P*=.55	0.61 (0.22–1.68)

Adjusted analyses reflect multivariable logistic regression with backward selection, including black race, age, body mass index, diabetes mellitus, chronic hypertension, previous full-term delivery, and previous preterm delivery.

aOR, adjusted odds ratio; *CI*, confidence interval; *GHTN*, gestational hypertension; *MD*, mean difference; *MVM*, maternal vascular malperfusion; *OR*, odds ratio.

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significantly associated with preterm birth risk (B, 3.77 [95% CI, 1.34–10.61; *P*=.01]).

The group with COVID-19, but not the COVID-19 vaccination group, was associated with a significantly higher rate of placental MVM (55.8% vs 35.8%; adjusted odds ratio [aOR], 2.34 [95% CI, 1.16–4.73]) and preterm birth (15.3% vs 6.6%; aOR, 4.54 [95% CI, 1.61–12.78]) than the control group (Table). Among 52 patients with COVID-19 during pregnancy and placental pathology available, 19 reported aspirin use. The rate of placental MVM was lower with the aspirin group, although not statistically significant (42.5% vs 63.6%; *P*=.13). In contrast, among 95 patients in the control group, the rate of placental MVM was higher in the aspirin group (48.5% vs 29.0%; *P*=.06), as expected based on baseline risk factors prompting aspirin use. There was no correlation between placental MVM and COVID-19 latency (greater or less than 30 days) ($r=-0.10$; *P*=.51).

CONCLUSION: COVID-19, but not COVID-19 vaccination, in pregnancy was associated with increased inflammatory cytokines, placental vascular pathology, and preterm delivery. This inflammatory signature, specifically TNFα, was correlated with preterm birth risk but not placental vascular pathology, suggesting potentially divergent pathways related to these downstream consequences. COVID-19 vaccination, despite mild viral-like symptoms, did not elicit the same pathologic effects, providing both pathophysiological and clinical evidence of safety of mRNA vaccines in pregnancy. Compared with a smaller study,[4] we did not identify a fetal inflammatory signature associated with COVID-19. There was likely undocumented COVID-19 exposure in the control or vaccination group,[3] although it would not be possible to determine if this exposure was before or during pregnancy, and if anything, this would lead to type 1 error. Further research is needed to elaborate on the pathophysiological basis for adverse perinatal outcomes following maternal COVID-19, timing of infection, and risk of these outcomes and how therapies, such as aspirin, may mitigate these downstream perinatal effects.[5] ■

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