Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

impact of BP Connect in gynecology clinics on timely primary care follow-up was almost identical to that seen in the rheumatology clinics where the intervention was initially developed and tested. Subsequent work will examine its impact on hypertension and CVD in more diverse populations and explore its impact when implemented at postpartum visits. ■

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

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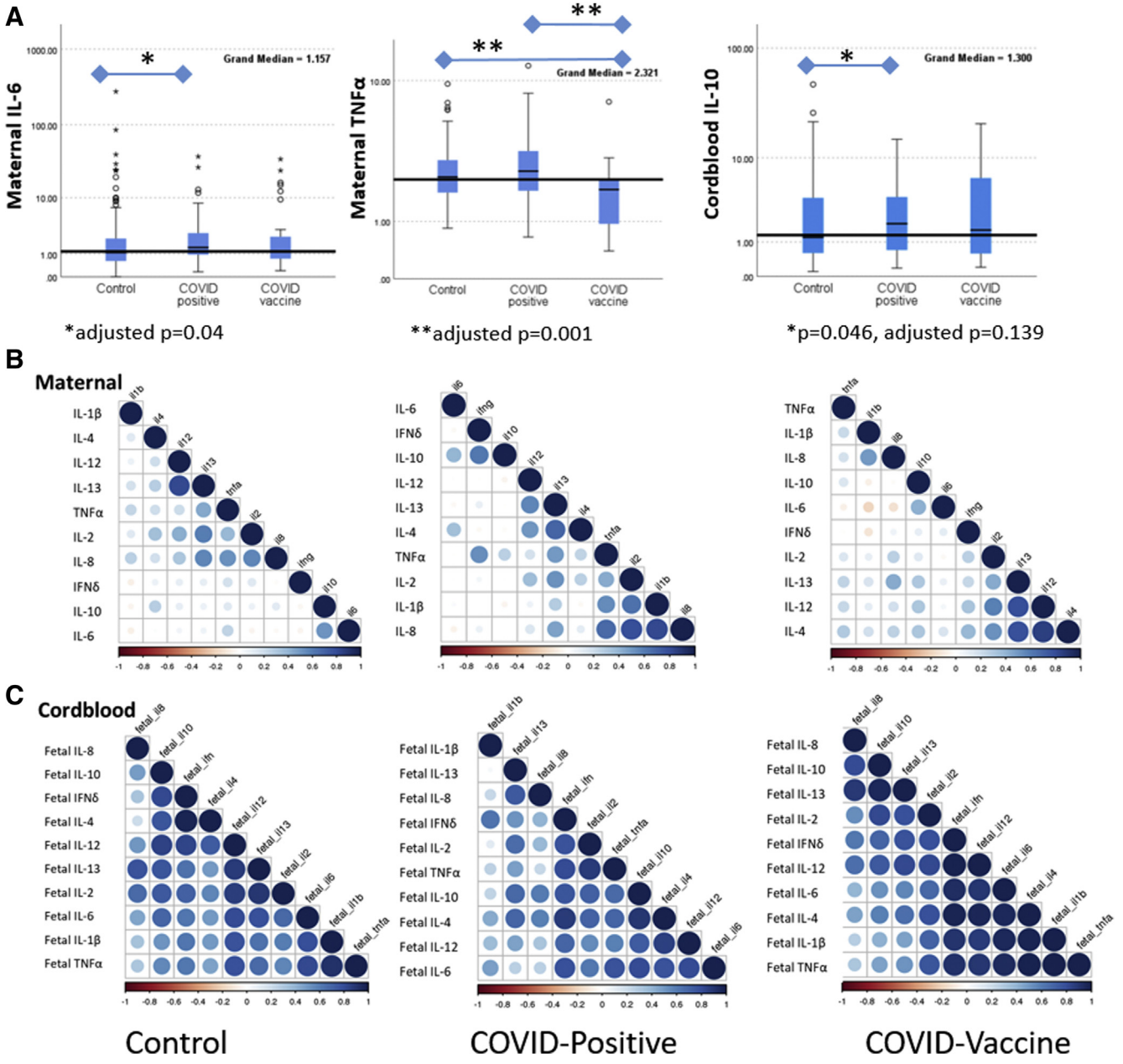
OBJECTIVE: COVID-19, even mild, is associated with a host inflammatory response,[1] which has not been well delineated in pregnancy. COVID-19 is associated with preterm birth,[2] preeclampsia,[2] and placental vascular pathology.[3] Although COVID-19 vaccination does result in mild viral-type symptoms 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

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.

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

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 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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Validation of childbirth-related posttraumatic stress disorder using psychophysiological assessment

OBJECTIVE: Posttraumatic stress disorder (PTSD) results from a specific, psychologically traumatic event (eg, war, accidents, or physical and/or sexual assaults). Increasing evidence indicates that childbirth and its associated circumstances can be experienced as a traumatic event and cause posttraumatic symptoms or even full PTSD.[1] This condition is not limited to pregnancy loss, stillbirth, and prematurity. It can develop after a full-term healthy birth, with an estimated prevalence between 4.6% and 6.3% and clinically significant symptoms in up to 16.8% of postpartum women.[1] Provisional diagnosis of maternal childbirth-related PTSD (CB-PTSD) primarily relies on the subjective report using questionnaires targeting PTSD, symptom severity (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) in the past month and resulting from childbirth as the index trauma.[1] Because some PTSD symptoms may overlap with other mental postpartum conditions (eg, depression),[2] we investigated whether CB-PTSD is characterized by the elevated psychophysiological reactivity observed in PTSD stemming from combat and other traumatic stressors.[3]

STUDY DESIGN: Overall, 34 women aged approximately 35 years, with an immediate postpartum Peritraumatic Distress Inventory score of >21, were recruited through hospital announcements. The average gestational delivery week was 38.76. Of note, 13 women with a subsequent PTSD Checklist for DSM-5 score of >43 were classified as having CB-PTSD; the remaining 21 women were classified as having no CB-PTSD (Table). The study was approved by the Mass General Brigham Human Research Committee. After giving written informed consent following a full explanation of the procedures, the patients were assessed using an established method that quantified skin conductance, heart rate, and left lateral frontalis and corrugator electromyogram responses during script-driven mental imagery of their childbirth experiences.

The primary analyses were univariate and multivariate analyses of variance. As an ancillary, a composite (univariate) measure of physiological responsivity was calculated as the "posterior probability" of a patient belonging to the PTSD reference group using an a priori discriminant function derived from a large sample of individuals with and without PTSD who had experienced other non−childbirth-related traumatic events and had undergone the same psychophysiological procedure.[4]

RESULTS: Participants with CB-PTSD were more physiologically responsive during imagery of their childbirth experiences than participants without CB-PTSD (Figure). Mean univariate physiological responses of the group with CB-PTSD were largely above working PTSD cutoffs (Figure, dotted lines) from previous studies of individuals exposed to other traumas, such as combat, sexual assaults, or motor vehicle accidents.[5] No significant physiological group difference was observed during imagery of a non−childbirth-related stressful event that was used as a control. Our findings suggest that patients with CB-PTSD exhibit physiological responses similar to individuals with other PTSDs.

CONCLUSION: This work provides a validation of the clinical reality of CB-PTSD diagnosis. In our study, women with CB-PTSD showed similarly elevated physiological responses during mental imagery of a traumatic childbirth experience as found in PTSD resulting from other types of traumas. Their physiological alterations were evoked by childbirth. Moreover, our findings encourage revising the formal recognition of mental illness with postpartum onset by expanding the spectrum to include disorders of traumatic stress. A simplified physiological assessment, performed during routine obstetrical care, of women showing clinically significant childbirth-related peritraumatic distress may aid