OBSTETRICS

Plasma and cerebrospinal fluid inflammatory cytokines in perinatal depression

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BACKGROUND: While perinatal depression is one of the most common complications of pregnancy, there is an insufficient understanding of the mechanistic underpinnings of disease. While an association between peripheral inflammatory cytokines and major depressive disorder has been demonstrated, cytokines cannot freely cross the blood-brain barrier, and thus, they give little insight into alternations in brain function. Because the brain is in direct communication with the cerebrospinal fluid, assessment of inflammation in the cerebrospinal fluid may be more directly related to the biologic markers of affective change.

OBJECTIVE: Our objectives were to examine the association between perinatal depression and inflammatory cytokines in plasma, the association between perinatal depression and inflammatory cytokines in cerebrospinal fluid, and the correlations between plasma and cerebrospinal fluid inflammatory cytokines.

STUDY DESIGN: This was a prospective, observational study of women with a singleton gestation at term undergoing a scheduled cesarean delivery. Women were screened for depression and those with depressive symptomatology preferentially enrolled. The Mini-International Neuropsychiatric Interview was administered to confirm the clinical diagnosis of depression. Maternal plasma and cerebrospinal fluid were collected preoperatively and cytokines measured via flow cytometry. Bivariable and multivariable analyses were used to determine the association between each cytokine and perinatal depression. Correlations were measured between the cytokines in plasma and cerebrospinal fluid.

RESULTS: Of the 117 women who met inclusion criteria, 76 (65%) screened positive for depression, 15 (20%) of whom met the clinical diagnostic criteria for depression. There were no significant associations between any of the plasma cytokines and perinatal depression in our sample. Conversely, in multivariable analyses, higher cerebrospinal fluid interleukin-1β (adjusted odds ratio, 232.7, 95% confidence interval, 5.9—9148.5), interleukin-23 (adjusted odds ratio, 22.1, 95% confidence interval, 1.7—294.5), and interleukin-33 (adjusted odds ratio, 1.7, 95% confidence interval, 1.1—2.6) concentrations were significantly associated with increased odds of perinatal depression. The plasma and cerebrospinal fluid cytokine concentrations were not strongly correlated.

CONCLUSION: Higher concentrations of cerebrospinal fluid cytokines were associated with perinatal depression. These cerebrospinal fluid cytokines were not strongly correlated with plasma cytokines, and accordingly, plasma cytokines were not significantly associated with perinatal depression. Central neuroinflammation, as opposed to peripheral inflammation, may represent a mechanistic pathway that contributes to perinatal depression.

Key words: antenatal depression, cerebrospinal fluid, cytokines, interleukin-1 beta, interleukin-23, interleukin-33, plasma

Depression is becoming increasingly recognized as a disorder of immune hyperactivation.[1–8] Patients with major depressive disorder have increased plasma inflammatory biomarkers, most consistently interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein.[9,10] Blockade of the production of these cytokines is associated with reduced depressive symptoms.[11–14] Studies in the perinatal period have suggested that postpartum depression is associated with increased plasma inflammatory biomarkers, most consistently IL-1β, soluble IL-1 receptor antagonist, and IL-6.[15–18]

While peripheral cytokines are able to cross the blood-brain barrier[1], equilibrium between cerebrospinal fluid (CSF) and plasma is not established and peripheral blood markers may not reflect the intracerebral environment milieu.[19] Although cytokines are large molecules, a variety of mechanisms facilitate transport between plasma and CSF. These include the following: (1) leaky regions of the blood-brain barrier, (2) active transport via various facilitative molecules, (3) activation of cells surrounding the cerebral vasculature, and (4) binding of cytokine receptors on peripheral afferent nerve fibers.[1]

When inflammatory cytokines are present in the CSF, they can cause damage to existing nerve cells as well as inhibition of neural cell growth in the hippocampus, amygdala, prefrontal cortex, anterior cingulate, and basal ganglia, which leads to symptoms of depression.[20] There is conflicting reported evidence between depressive symptomatology and CSF inflammatory biomarkers (Table 1). Heterogeneity in research methodology, including indications and circumstances for undergoing a lumbar puncture, may explain some of these reported differences.

Pregnancy further complicates the inflammatory assessment because normal pregnancy represents a state of immunologic changes. As pregnancy progresses, increases in peripheral phagocytic (monocytes and granulocytes) and dendritic cells have been observed that are partially offset by decreases in CD4, CD8, B, and NK cells.[21]

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AJOG at a Glance

Why was this study conducted?

Major depression outside pregnancy can be a disorder of immune hyperactivation. Peripheral cytokines are large molecules that cannot freely cross the blood-brain barrier and may not reflect the intracerebral milieu. Assessment of inflammation in the cerebrospinal fluid (CSF) is more directly related to biologic markers of affective change and may inform the pathophysiology of perinatal depression.

Key findings

In multivariable analyses, higher CSF concentrations of interleukin (IL)-1β, IL-23, and IL-33 were associated with an increased risk for perinatal depression.

What does this study add to what is known?

Plasma and CSF inflammatory cytokines are not correlated in pregnant women. While plasma inflammatory cytokines are not associated, CSF IL-1β, IL-23, and IL-33 are associated with perinatal depression. Further exploration of the neurobiologic mechanisms of perinatal depression is necessary to facilitate biomarker development and identify novel treatment targets.

Correspondingly, plasma cytokines and chemokines involved in phagocytic recruitment, such as TNFα, increase, whereas plasma inflammatory molecules, such as vascular endothelial growth factor and interferon (IFN)-γ decrease throughout gestation.[22]

Despite these changes, perinatal depression has been shown to be associated with increased plasma inflammatory cytokines, similar to major depressive disorder outside pregnancy.[15–18] The association between depressive symptomatology and CSF inflammatory cytokines has not been well established in pregnant patients. A positive correlation between CSF IL-6 and TNFα and scores on the Edinburgh Postnatal Depression Scale has been reported in parturients; however, the authors did not account for the potential underlying impact of labor itself or establish clinical diagnoses of major depressive disorder.[23]

Perinatal depression, or depression that begins either during pregnancy or within 12 months postpartum, is one of the most common complications of pregnancy affecting approximately 1 in 7 women.[24,25] However, the majority of women with depression are neither identified nor treated.[26,27] This disparity between clinical need and care provision is not due to a lack of access to the health care system in general because contact with health care professionals is typically increased in the perinatal period. The unmet need reflects barriers to mental health care.[27] Furthermore, current treatments are not often fully effective, and only a minority of women achieve a therapeutic response.[26,27]

Defining the mechanistic underpinnings of perinatal depression, including the role of inflammation, is critical to developing more effective interventions. To address this gap in knowledge, we examined the association between both plasma and CSF inflammatory cytokines and perinatal depression. We hypothesized that women with perinatal depression would exhibit higher concentrations of inflammatory cytokines in the plasma and CSF compared with euthymic women.

Materials and Methods

Overview

This prospective observational study aimed to compare inflammatory cytokines in simultaneous plasma and CSF samples from women at term with and without an antenatal major depressive episode. A second aim was to determine whether inflammatory cytokines in the plasma or CSF correlate with later postpartum depressive symptomatology. The third aim was to assess the correlation between CSF and maternal plasma inflammatory cytokines. The Northwestern University Institutional Review Board approved this study, and all women provided written informed consent.

Subjects

Women with singleton, term gestations who were undergoing a scheduled cesarean delivery were eligible for participation. Women in labor (either clinically diagnosed, self-reported to have regular painful contractions, or endorsing leakage of fluid) were excluded because of the potential of the parturition process to alter markers of inflammation obtained at the time of epidural or spinal placement. Similarly, women with diabetes or preeclampsia were excluded because of their potential to confound observed associations, given their relationship with depression[28,29] and their inflammatory underpinnings.[30] Women also were excluded if they were younger than 18 years old, had diagnosed anomalies in their fetuses, were living with HIV, or were taking antiinflammatory medications (eg, steroids, nonsteroidal antiinflammatory drugs) within 2 weeks of delivery. For this analysis, women treated with antidepressants also were excluded because of the antiinflammatory effects of these medications.[31–35]

Measures and procedures

Women who presented for a scheduled cesarean delivery were approached upon admission for surgery and, after consent was obtained, screened for depression using the Inventory of Depressive Symptomatology-Self-Report (IDS-SR_{30}). The IDS-SR_{30} is a depression screen with excellent psychometric properties,[36] with a reported sensitivity of 78% and specificity of 76% for prenatal depression.[37]

The IDS-SR_{30} asks questions about depressive symptoms over the preceding week and is a valid screen for antenatal depression when administered prior to delivery. The IDS-SR_{30} was used to identify women with moderate to severe depressive symptoms to enrich the sample for women with clinical evidence of a major depressive episode. One screen-negative (IDS-SR<18) woman

TABLE 1
Prior studies examining the association between depression and cerebrospinal fluid inflammatory biomarkers outside pregnancy

Author	Comparison	CSF changes
Janelidze et al[48]	Suicide attempters with anxiety vs healthy controls	IL-8 decreased
Bay-Richter et al[49]	Suicide attempters vs healthy controls	IL-6 increased
Kern et al[50]	Geriatric women with and without depression	IL-6 and IL-8 increased
Lindqvist et al[51]	Parkinson's disease with and without depression	CRP and MCP-1 increased
Erhardt et al[52]	Suicide attempters vs healthy controls	IL-6 increased
Sasayama et al[53]	People with MDD vs healthy controls	IL-6 increased
Isung et al[54]	Suicide attempters vs healthy controls	IL-8 decreased
Martinez et al[55]	People with MDD vs healthy controls	IL-1, IL-6, and TNF-α increased
Lindqvist et al[19]	Suicide attempters vs healthy controls	IL-6 increased
Raison et al[56]	People receiving IFN with and without depression	IL-6 and MCP-1 increased
Carpenter et al[57]	MDD vs healthy controls	No change in IL-6 levels
Levine et al[58]	MDD vs healthy controls	IL-1β increased, IL-6 decreased, no change in TNF-α
Stubner et al[59]	Geriatric individuals with and without MDD	IL-6 decreased
Hestad et al[60]	People with neurologic complaints with and without depression	No changes in CSF cytokines

CRP, C-reactive protein; *CSF*, cerebrospinal fluid; *IFN*, interferon; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *MDD*, major depressive disorder; *TNF*, tumor necrosis factor.
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was enrolled for every 2 screen-positive women (IDS-SR$\geq$18) who were identified. An IDS-SR score above 11 signifies mild depression, whereas a score above 23 signifies moderate depression.

The choice of 18 as a cutoff was made to enrich the sample with women who had more significant symptomatology to ensure an adequate sample of women with clinical major depressive disorder for analysis. A member of the research team, trained and supervised by a perinatal psychologist, administered the Mini-International Neuropsychiatric Interview (MINI, version 5.0.0) in all enrolled women as the gold standard used to confirm the clinical diagnosis of an active antenatal major depressive episode as well as to identify any other *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, psychiatric diagnoses.

While establishing intravenous access, 15 mL of maternal blood was drawn; this sample was centrifuged at −4°C to obtain plasma, which was immediately stored at −80°C. At the time of spinal analgesia administration, 2 mL of CSF was aspirated prior to anesthetic injection and immediately stored at −80°C. Both plasma and CSF samples were assayed in duplicate using flow cytometry and a multiplex bead-based assay panel for 13 inflammatory cytokines/chemokines including IL-1β, IFN-α, IFN-γ, TNF-α, monocyte chemotactic protein (MCP)-1, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33 (LEGENDplex; BioLegend, San Diego, CA).

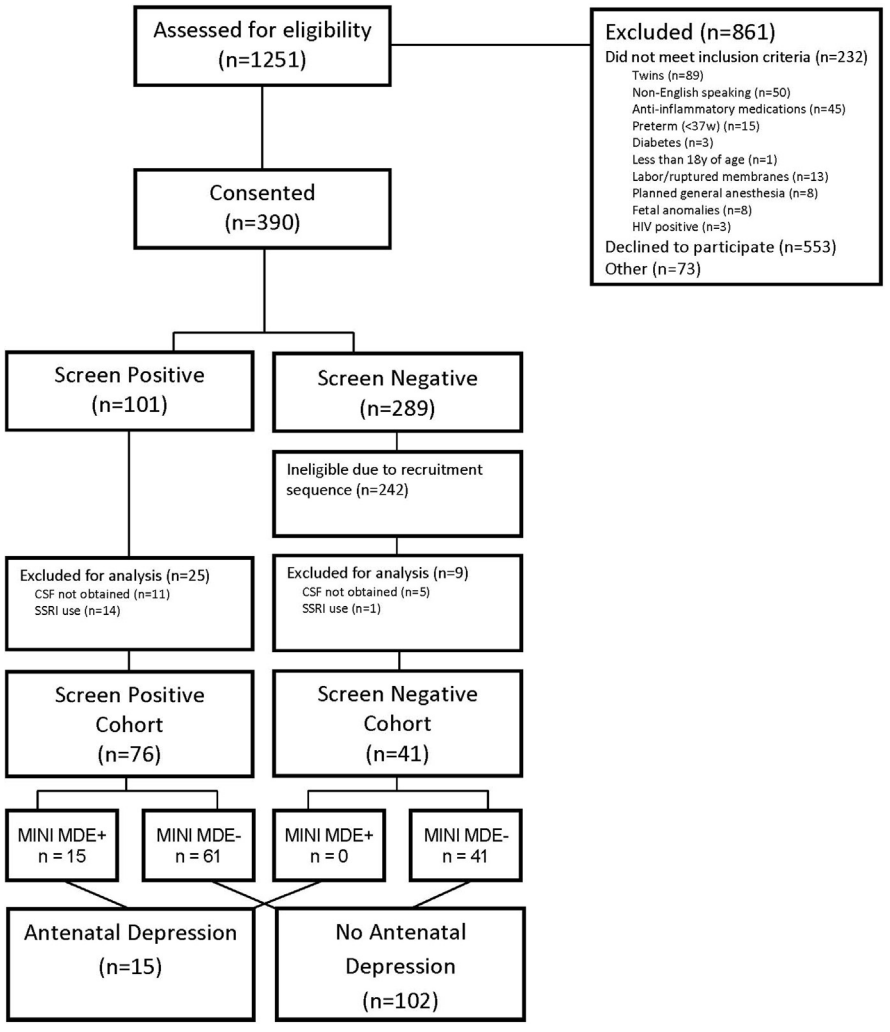
This panel was chosen because it includes cytokines previously associated with major depressive disorder or perinatal depression in the existing literature.[9,10,23] Characteristics of the assay, including sensitivity and cross-reactivity are available online.[38] The minimum detectable concentration in serum has been reported to be between 0.6 and 1.9 pg/mL for each of the examined cytokines. Each sample was tested in triplicate and each sample was run twice in independent assays. The assay used monoclonal antibodies that have been well characterized and have no known cross-reactivity.

On postpartum day 1, self-reported surveys were administered to collect sociodemographic characteristics. In addition, members of the research team abstracted the medical and obstetric history from the electronic medical records with quality control via spot checks performed by another investigator (E.S.M.). An assessment of perceived stress, measured using Cohen's Perceived Stress Scale (PSS), was obtained,[39] given the established relationship between stress and inflammatory cytokines.[40,41] Women were contacted via electronic mail between 4 and 8 weeks postpartum, at which time they were asked to complete a follow-up IDS-SR_{30}.

Statistical analyses

Women were stratified by the diagnosis of a current antenatal major depressive episode (MDE). Sociodemographic and clinical characteristics, as well as PSS scores, were compared across these 2 groups using χ^2, Fisher exact, or Mann-Whitney *U* tests as appropriate. Plasma and CSF cytokine concentrations were compared between women with and

FIGURE
Study flow chart



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without an MDE using Mann-Whitney *U* tests. Plasma and CSF cytokines that differed between women with and without an MDE at the 20% level of significance (ie, $P < .20$) were entered into multivariable logistic regression models for the outcome of MDE. Potential confounders were identified using the change in estimate criteria of 10%, in which variables that altered the unadjusted exposure-outcome association by 10% or more were included in multivariable models to establish whether each assayed plasma or CSF cytokine was independently associated with the presence of an MDE.

Analyses further involved Spearman's sample correlation coefficients of the entire cohort to evaluate a potential relationship between cytokine concentrations and antenatal depressive symptomatology (IDS-SR score). A subscale of the IDS-SR allowed for assessment of the presence of symptoms ascribed to the inflammatory subtype of depression (atypical depression),[13] and Spearman's correlations were used to estimate the association between cytokine concentrations and atypical depressive symptoms. Spearman's correlations were used to estimate the associations between the cytokine concentrations and the postpartum IDS-SR score. Finally, Spearman's correlations between CSF and maternal plasma inflammatory cytokines were also estimated. Analyses were performed using Stata version 14.0 (StataCorp, College Station, TX). Tests were all 2 tailed and, unless otherwise specified, assumed a 5% level of statistical significance. We did not adjust *P* values to account for multiple hypothesis tests.

Results

Cohort characteristics

Of the 1251 women approached for eligibility, 390 consented to participate. After excluding those who did not have biospecimen obtained or who were using an selective serotonin reuptake inhibitor, 117 participants were enrolled between March 2014 and June 2016 in the final sample (Figure). Of the 76 women who endorsed at least moderate depressive symptomatology on the IDS-SR_{30} (IDS-$SR_{30} \geq 18$), 15 (20%) had an MDE based on the MINI evaluation. Of these 15 women, 14 (93%) had a comorbid anxiety disorder, and 6 (40%) had a history suggestive of possible bipolar disorder based on their MINI evaluation.

Of the 61 screen-positive women who did not have an MDE, 11 (18%) had an active anxiety disorder and 4 (5%) had a history of possible bipolar disorder based on their MINI evaluation. The remainder of women had subclinical depressive symptoms, given the absence of diagnostic criteria for a major depressive episode.

Baseline characteristics of the cohort stratified by the presence of an MDE determined by the MINI are shown in Table 2. Compared with women not experiencing an MDE, women with an MDE tended to be younger, have a lower household income, have a higher body mass index at delivery, have a lower level of education, and were more likely to be non-Hispanic black. Women with an MDE also had higher levels of perceived stress.

Antenatal depression and cytokines

The standard curve for each cytokine was 2−10,000 pg/mL. Prior to testing any clinical samples, recombinant IL-6, IL-8, and IFN gamma were purchased and titered into 3 independent plasma and CSF samples for assay. The calculated curves ([plasma or CSF + cytokine] − [plasma or CSF alone]) for all 3 cytokines were as expected, indicating that the assay performed as described in

TABLE 2
Sociodemographic and clinical characteristics of the cohort, stratified by depression status

Characteristics	MDE negative (n = 102)	MDE positive (n = 15)	*P* value
Maternal age, y	35.3 ± 3.7	33.1 ± 5.5	.045
Race/ethnicity			.014
Non-Hispanic white	75 (73.5%)	8 (53.3%)	
Non-Hispanic black	8 (7.8%)	6 (40.0%)	
Hispanic	14 (13.7%)	1 (6.7%)	
Other/unknown	5 (4.9%)	0 (0.0%)	
Education			.031
Completed college	90 (88.2%)	10 (66.7%)	
Some college/trade school	10 (9.8%)	3 (20.0%)	
High school or less	2 (2.0%)	3 (13.3%)	
Employed	90 (88.2%)	12 (80.0%)	.407
Married	93 (91.2%)	11 (73.3%)	.063
Household income			.006
<$40,000	9 (8.8%)	1 (6.7%)	
$40,000–79,000	5 (4.9%)	5 (33.3%)	
≥$80,000	88 (86.3%)	9 (60.0%)	
Nulliparous	22 (21.6%)	1 (6.7%)	.297
BMI at delivery, kg/m^2	31.1 (27.3–34.0)	33.6 (29.2–43.2)	.026
Gestational weight gain, lb	33.7 ± 10.8	35.9 ± 10.3	.464
Gestational weight gain >35 lb	38 (37.3%)	9 (60.0%)	.093
Tobacco use (ever)	18 (17.7%)	4 (26.7%)	.478
GA at delivery	39.3 (39.0–39.6)	39.0 (39.0–39.3)	.084
≥39 wks at delivery	90 (88.2%)	14 (93.3%)	.557
Indication for cesarean delivery			.747
Repeat	76 (74.5%)	13 (86.7%)	
Fetal malposition	12 (11.8%)	1 (6.7%)	
Placenta previa	1 (1.0%)	0 (0.0%)	
Other	13 (12.8%)	1 (6.7%)	
PSS score	19 ± 7	30 ± 7	< .001

Data are reported as mean ± SD, n (percentage), or median (interquartile range).

BMI, body mass index; *GA*, gestational age; *MDE*, major depressive episode; *PSS*, Perceived Stress Scale.

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the presence of plasma or CSF. No cross-reactivity was detected.

Empiric distributions of plasma and CSF cytokines were highly skewed (assessed using the Shapiro-Wilk normality test) despite attempted transformations (including cubic, square, square root, log, 1/square root, inverse, 1/square, and 1/cubic transformations); therefore, analyses involved nonparametric methods. IL-1β and IL-33 were below the limits of detection in the plasma. There were no significant differences in plasma cytokines between women with and without an MDE (Table 3). Aside from IL-6, point estimates for all measured CSF inflammatory cytokines were higher in women experiencing an MDE compared with those without an MDE, although none of these differences reached statistical significance (Table 3). A post hoc power calculation, using an alpha of 0.05, demonstrated that we had 80% power to identify a 1.8-, 1.3-, and 1.4-fold change in CSF IL-1β, IL-6, and TNF-α, respectively, associated with a major depressive episode.

Because CSF IL-1β, IL-18, IL-23, and IL-33 were associated with an MDE at a significance level less than .2, they were included in the planned multivariable analyses. IL-1β, IL-23, and IL-33 all were significantly associated with an MDE after controlling for potential confounders (Table 4).

Antenatal depressive symptomatology and cytokines

There were no significant correlations between antenatal IDS-SR scores and any plasma or CSF cytokine (Table 5).

Atypical depression

There was a weak correlation between atypical depression and plasma IFN-γ but no significant correlation between any of the other plasma or CSF cytokines and the IDS-SR$_{30}$ atypical depression scores (Table 6). These findings were unchanged when women with other psychiatric comorbidities were excluded from analysis (data not shown).

Postpartum depressive symptomatology

Of the 117 women who met inclusion criteria, 90 (77%) completed a postpartum IDS-SR$_{30}$: 46 (51%) with no, 34 (38%) with mild, 9 (10%) with moderate, and 1 (1%) with severe depressive symptoms. There was an observed weak correlation between plasma IL-10 and postpartum depressive symptomatology, but no other significant correlations between postpartum IDS-SR scores and the measured plasma or CSF inflammatory cytokines (Table 6).

Correlations between plasma and CSF cytokines

Plasma IL-6, IL-8, IFN-γ, and MCP-1 were not significantly correlated with their corresponding CSF cytokines. While

TABLE 3
Bivariable analyses of plasma and cerebrospinal fluid cytokines stratified by perinatal depression status

	Plasma			CSF		
Variables	MDE negative	MDE positive	*P* value	MDE negative	MDE positive	*P* value
IL-1β	—	—	—	0.49 (0.32–0.79)	0.79 (0.49–1.00)	.062
IL-6	3.05 (1.81–6.39)	1.81 (1.74–6.14)	.283	2.32 (1.89–2.97)	2.43 (1.60–2.67)	.481
IL-8	2.28 (1.76–3.73)	2.28 (1.30–5.59)	.955	110.91 (91.72–131.74)	100.49 (95.50–114.94)	.268
IL-10	1.92 (1.58–2.34)	1.92 (1.58–2.34)	.795	—	—	—
IL-12p70	1.95 (1.55–2.44)	1.95 (0.65–2.44)	.990	—	—	—
IL-17a	2.53 (1.60–6.36)	2.53 (1.60–4.89)	.922	—	—	—
IL-18	167.74 (119.24–242.81)	140.26 (110.76–239.46)	.660	0.90 (0.63–1.10)	1.10 (0.63–1.10)	.167
IL-23	2.60 (2.16–6.94)	2.60 (2.16–5.39)	.589	1.01 (0.97–1.04)	1.04 (0.97–1.07)	.161
IL-33	—	—	—	4.19 (1.92–5.67)	4.33 (4.06–5.67)	.179
IFN-α	2.07 (1.95–4.01)	2.10 (1.95–6.55)	.813	—	—	—
IFN-γ	4.93 (3.18–9.49)	4.53 (3.18–9.49)	.784	1.62 (1.45–2.54)	2.25 (1.01–4.42)	.700
TNF-α	1.82 (1.45–2.22)	1.82 (1.75–2.22)	.925	0.93 (0.33–1.15)	1.04 (0.88–1.15)	.290
MCP-1	267.49 (193.70–367.30)	247.89 (173.36–68.24)	.594	971.80 (800.81–1135.92)	1094.16 (745.67–1203.80)	.361

Data are presented as median (interquartile range) in picograms per milliliter.

CSF, cerebrospinal fluid; *IFN*, interferon; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *MDE*, major depressive episode; *TNF*, tumor necrosis factor.

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IL-18, IL-23, and TNF-α did exhibit statistically significant correlations between plasma and CSF concentrations, these relationships were all weak (Table 7).

Comment

Findings and proposed pathophysiology

In term pregnant women, CSF concentrations of IL-1β, IL-23, and IL-33 are increased in the setting of an active major depressive episode. IL-1β and IL-33 are both in the IL-1 family of cytokines and may be mechanistically linked with antenatal depression via associated alterations in tryptophan metabolism.[42]

Tryptophan is the precursor to serotonin, a monoamine whose production is critical to mood stability. Th1-cytokines, such as the IL-1 family of cytokines, induce expression of indolamine-2,3-dioxygenase, which degrades tryptophan into its catabolites (ie, kynurenine and quinolinic acid). Not only does the breakdown of tryptophan yield a state of relative serotonin depletion, but these catabolites have also been shown to independently induce depressive and anxiety symptoms.

IL-23 has received less study in the pathogenesis of depression. IL-23 is a proinflammatory cytokine involved in the differentiation of Th17 lymphocytes.[43] In this role, IL-23 has recently been recognized as essential in the development of autoimmunity, and trials of antibodies to IL-23 for the treatment of psoriasis, rheumatoid arthritis, and Crohn's disease are underway.[44] Based on our results along with the promising preliminary findings in other disease states with a dysregulated inflammatory system, further investigation of the role of Th17 lymphocytes and the IL-23 immune axis in the pathophysiology of depression is warranted.

Comparison to existing literature

In contrast to the CSF findings, plasma concentrations of inflammatory cytokines were not associated with depressive symptomatology, atypical depressive symptomatology, or an active major depressive episode. These findings differ from previous reports.[15–18] One reason for this discrepancy might be that this investigation excluded women who have experienced antenatal inflammatory conditions such as preterm labor, preeclampsia, or diabetes. Perhaps by systematically excluding women with these complications, we selected a subgroup of antenatal depression that did not have an inflammatory phenotype.

To the best of our knowledge, there is only 1 prior manuscript assessing CSF cytokines and postpartum depressive symptomatology. Boufidou et al[23] demonstrated a positive association between the two CSF cytokines examined, IL-6 and TNF-α, and depressive mood symptoms in the first 4 days postpartum. While we did not identify significant correlations between these cytokines and postpartum depressive symptomatology, as described in the previous text, our restrictive inclusion criteria may have masked an association that may be present in a more generalized population.

Strengths and limitations

The results of our study are strengthened by the use of the MINI to achieve a

TABLE 4
Multivariable analyses for the outcome of a major depressive episode

Variables	aOR[a]	95% CI
CSF IL-1β	232.7	5.9–9148.5
Non-Hispanic black race	17.8	1.9–169.0
Nulliparous	0.03	0.01–0.05
Gestational age at delivery, wks	0.4	0.1–1.3
PSS score	1.4	1.2–1.6
CSF IL-23[b]	22.1	1.7–294.5
BMI at delivery, kg/m^2	1.2	1.0–1.3
PSS score	1.3	1.1–1.5
CSF IL-33[b]	1.7	1.1–2.6
Maternal age, y	0.9	0.7–1.0
Nulliparous	0.2	0.1–2.0
PSS score	1.3	1.1–1.5

aOR, adjusted odds ratio; *BMI*, body mass index; *CI*, confidence interval; *CSF*, cerebrospinal fluid; *IL*, interleukin; *PSS*, Perceived Stress Scale.

[a] Adjusted for the listed potential confounders; [b] represents 3 separate multivariable analyses.

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diagnosis of perinatal depression. Another strength of this study is the exclusion of women in labor, which avoided potential parturitional alterations in inflammation. While this strengthens our confidence in the observed association between inflammatory markers and perinatal depression, our findings may not be generalizable. A significant number of approached women (553, 44%) declined to participate. Furthermore, because inflammatory cytokines are increased in women who undergo spontaneous preterm labor, our inclusion criteria (women who had not entered spontaneous labor and were at term) may have selected a subset of women with less systemic inflammation.

Each of these characteristics of the study sample may limit the generalizability of the findings when applied to the broader obstetric population. In addition, we do not have data on the serum/CSF albumin ratio, which has been postulated to impact CSF concentrations of cytokines[45] and may be influenced by inflammatory mechanisms.[46]

Another limitation is that, given the relatively small sample size of women with an active MDE, bivariable analyses between cytokines and perinatal depression were not significant and our multivariable models may be oversaturated. While this should raise some caution when interpreting the results, the consistent association between IL-1β, IL-23, and IL-33 concentrations and MDE in both bivariable and multivariable analyses supports the veracity of this relationship.

Similarly, because of the relatively small sample size, convergence could not be achieved when attempting to fit the data into a log-linear model, and thus, a logistic regression with its associated odds ratio is reported. Consequently, the magnitude of the observed associations in the multivariable analyses may be slightly lower than those reflected in the reported odds ratios.

Finally, given their antiinflammatory effects,[31–35] this study excluded women with perinatal depression taking antidepressant medications, and the results may not apply to them. However, because the majority of women with perinatal depression in the United States do not receive treatment,[27,47] we believe that this exclusion results in applicability to many women with major depressive disorder and is more reflective of the

TABLE 5
Correlations between cerebrospinal fluid cytokines and antenatal depressive symptomatology

	Antenatal IDS-SR score	
Variables	Spearman's rho	*P* value
Plasma IL-6	0.01	.925
Plasma IL-8	0.14	.127
Plasma IL-10	0.03	.783
Plasma IL-12p70	0.06	.542
Plasma IL-17a	0.05	.634
Plasma IL-18	0.10	.277
Plasma IL-23	−0.01	.895
Plasma IFN-α	0.01	.972
Plasma IFN-γ	0.16	.084
Plasma TNF-α	0.05	.573
Plasma MCP-1	0.15	.118
CSF IL-1β	0.01	.890
CSF IL-6	0.06	.533
CSF IL-8	0.01	.910

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TABLE 5
Correlations between cerebrospinal fluid cytokines and antenatal depressive symptomatology *(continued)*

	Antenatal IDS-SR score	
Variables	Spearman's rho	*P* value
CSF IL-18	−0.06	.496
CSF IL-23	0.01	.888
CSF IL-33	0.02	.792
CSF IFN-γ	0.08	.398
CSF TNF-α	0.03	.719
CSF MCP-1	0.07	.439

CSF, cerebrospinal fluid; *IDS-SR*, Inventory of Depressive Symptomatology-Self Report; *IFN*, interferon; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *TNF*, tumor necrosis factor.

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TABLE 6
Correlations between plasma cerebrospinal fluid cytokines and depressive symptomatology

	Antenatal atypical depression score		Postpartum IDS-SR score	
Variables	Spearman's rho	*P* value	Spearman's rho	*P* value
Plasma IL-6	−0.05	0.598	−0.11	.288
Plasma IL-8	0.18	0.054	0.01	.909
Plasma IL-10	0.11	0.240	0.22	.037
Plasma IL-12p70	0.20	0.031	0.14	.197
Plasma IL-17a	−0.01	0.961	0.15	.161
Plasma IL-18	0.11	0.234	0.02	.836
Plasma IL-23	−0.04	0.689	−0.18	.085
Plasma IFNα	−0.09	0.368	−0.05	.628
Plasma IFNγ	0.21	0.024	0.17	.109
Plasma TNFα	−0.06	0.501	−0.05	.673
Plasma MCP-1	0.09	0.318	0.06	.570
CSF IL-1β	0.08	0.390	−0.04	.724
CSF IL-6	−0.04	0.707	0.07	.529
CSF IL-8	−0.02	0.797	0.05	.672
CSF IL-18	−0.10	0.302	0.02	.828
CSF IL-23	0.06	0.545	0.01	.924
CSF IL-33	−0.03	0.766	0.11	.316
CSF IFNγ	0.01	0.960	−0.05	.621
CSF TNFα	−0.03	0.787	0.18	.086
CSF MCP-1	0.01	0.926	0.04	.678

CSF, cerebrospinal fluid; *IDS-SR*, Inventory of Depressive Symptomatology-Self-Report; *IFN*, interferon; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *TNF*, tumor necrosis factor.

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pathophysiology underlying major depressive disorder.

Depressive symptomatology

We were unable to identify a dose-response relationship between antenatal depressive symptomatology and CSF inflammatory cytokines, which raises caution in interpreting the observed associations. One explanation could be a threshold effect of inflammation that yields overt depression (defined by the MINI) and that subclinical depressive symptoms (ie, women with a positive $IDS\text{-}SR_{30}$ but a negative screen for a major depressive episode on the MINI) represent a separate pathophysiology.

Alternatively, as evidenced by the discordance between the IDS-SR screen results and the diagnostic findings on the MINI, the heterogeneity of diagnoses uncovered by a positive IDS-SR (eg, anxiety, bipolar disorder) biases correlations between overt depressive symptomatology and inflammatory cytokines toward the null. In addition, there was not a strong correlation between postpartum depressive symptomatology and any of the measured plasma or CSF inflammatory cytokines. This suggests that any observed cytokine alterations are a transient finding and not a harbinger for future depressive symptoms.

Implications of the findings

Notably, we identified a lack of strong correlation between plasma and CSF inflammatory cytokines. The discrepancy between plasma and CSF cytokines emphasizes the critical need for paired CSF and plasma for biomarker development research and novel therapeutic development in the field of perinatal depression. Specific focus should be paid to the pathophysiologic mechanisms that may link CSF IL-1β, IL-23, and IL-33 concentrations with development of a MDE.

Conclusion

In conclusion, CSF concentrations of the inflammatory cytokines IL-1β, IL-23, and IL-33 are independently associated with an MDE in pregnant women at term. These findings support a neuroinflammatory mechanism for perinatal

TABLE 7
Correlations between cerebrospinal fluid and plasma cytokines

Variables	Spearman's rho	*P* value
IL-6	−0.03	.751
IL-8	−0.01	.950
IL-18	0.37	< .001
IL-23	0.31	< .001
IFNγ	0.07	.465
TNFα	0.21	.026
MCP-1	−0.05	.598

IL, interleukin; *IFN*, interferon; *MCP*, monocyte chemotactic protein; *TNF*, tumor necrosis factor.

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depression. If confirmed, these findings would support future research on adjunctive antiinflammatory agents to reduce depressive symptomatology during pregnancy. ■

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