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Is There an Inflammatory Profile of Perinatal Depression?

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Abstract

Purpose of Review To synthesize and critically examine recent evidence regarding associations between immune system activity and perinatal depression.

Recent Findings Despite a significant number of studies assessing potential immunological markers of perinatal depression, it does not appear that levels of any individual pro- or anti-inflammatory marker is a useful predictor of perinatal depression. Some recent studies have observed differences in overall immune system functioning and adaptation across this period, taking into account multiple pro- and anti- inflammatory markers. Furthermore, there is evidence for interactions between depression and maternal psychosocial factors. Immune system functioning may be a mechanism through which social determinants of health contribute to risk for perinatal depression.

Summary There is substantial evidence implicating dysregulated immune activity in perinatal depression, yet little clarity regarding a consistent immune profile, especially based on analysis of circulating peripheral cytokines.

Keywords Inflammation · Immune · Depression · Pregnancy · Postnatal depression

Introduction

Perinatal mood disorders are among the most common birth complications, affecting nearly 700,000, or 1 in 5 women annually [1–3]. The consequences of perinatal depression are enduring and costly for both mother and child, ranging from reduced quality of life and loss of resources, negative effects on caregiving and compromised child development, to maternal suicide, which accounts for 20% of postpartum deaths [2]. Evidence from epidemiological studies point to clear risk factors for perinatal depression, including reduced social support, prior history of major depression, younger age, history of interpersonal trauma, prior pregnancy loss, and socioeconomic stress [3, 4]. Though clear causal mechanisms have not been determined, a combination of and interaction among social, environmental, and biological factors is likely to contribute to the etiology of perinatal depression. Altered immune activity is a compelling mediator between these factors and may explain consistently observed associations between physical and mental health [5], particularly during the peripartum, which is a period of immune modulation. Building on evidence that inflammation is involved in the pathogenesis of major depression in non-pregnant adults [6, 7], and given the dynamic nature of the immune system over the peripartum, there is strong theoretical basis to explore immune dysregulation as part of the neurobiological profile of perinatal depression [8]. The aim of this review is to synthesize and critically examine recent evidence regarding associations between immune system activity and perinatal depression.

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The Functioning Immune System in Health and Healthy Pregnancy

Immune system functioning is essential in protecting the body and maintaining homeostasis through responding to different external and internal stimuli. Briefly, the immune system is composed of two parts: innate and adaptive

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systems, which work together to efficiently respond to challenges and protect the body from insults (Reviewed in [9]). The innate immune system includes macrophages, natural killer cells, mast cells, dendritic cells, monocytes, and granulocytes, which patrol the circulation for cell damage and pathogens and provide a rapid response. It also recruits the adaptive immune system, which is composed of B and T lymphocytes that later differentiate to express antigen-specific receptors. This specificity accounts for the slower response of the adaptive immune system relative to the innate. When activated, T-cells may become either cytotoxic ($CD8^+$ cells), helper (Th cells), or regulatory T cells (Tregs). These immune cells will secrete cytokines and chemokines to facilitate the recruitment and differentiation of the different subtypes of immune cells. Th cells including Th1, Th2, and Th17 have been studied in the context of depression by examining their key effector cytokines, IFN-γ, IL-4, and IL17A, respectively [9, 10]. While Th1 cells are involved in targeting intracellular pathogens and autoimmunity, Th2 functions to target extracellular pathogens and are involved in allergic reactions [10]. On the other hand, $CD8^+$ cells eliminate infected cells and Tregs negatively regulate immune responses to ensure limited activation protecting against autoimmunity [10].

To better understand the role of inflammation in perinatal depression, it is essential to first review inflammation as part of the physiological changes that takes place in healthy pregnancy. Earlier views described pregnancy as a condition with a suppressed immunity, however more recent evidence indicates that this is a period of a complex immunological adaptation and modulation that ensures successful implantation, fetal growth, and parturition [11, 12]. Locally in the uterus and placenta, immunological status goes through changes across gestation. During the first trimester, cytokines including, IL-6, IL-1β, IL-8, and TNF-α, are released by the endometrial cells and recruit immune cells to the site of implantation, facilitating a pro-inflammatory environment for the implantation of the embryo resembling a process of wound healing [13]. However, this is accompanied with Treg cells release of anti-inflammatory factors such as IL-10 to limit inflammation [14, 15]. This later is shifted into an anti-inflammatory status in the 2^{nd} trimester, during which the fetus is growing. In preparation for parturition during the 3^{rd} trimester, a proinflammatory microenvironment is stimulated by an increased influx of immune cells facilitating labor [11, 12]. There are reports of increased systemic innate immunity during pregnancy with increased responses of monocytes, neutrophils, and natural killer cells to stimulation [16]. While T cells counts do not change across gestation, they are lower during pregnancy compared to non-pregnant women [14, 17]. However, there is a known shift in the subsets of Th cells from intracellular responses by Th1 cells to humoral responses by Th2, measured by the ratio of Th1/Th2 and their effector cytokines IFN-γ/IL-4 [14]. Others have reported an overall reduction in pro-inflammatory cytokine trajectories during pregnancy in both innate and adaptive, specifically Th1, immunity, and an increase in anti-inflammatory responses indicated by IL-10 levels [15].

Associations Between Inflammatory Markers and Perinatal Depression

To date, to identify potential immunological biomarkers of perinatal depression, the majority of research has focused on measuring peripheral levels of select cytokines and other circulating inflammatory markers in patients with perinatal depression, or correlating levels of markers with symptom severity. While this approach offers only indirect assessment of neuroimmune activity, blood samples are convenient biospecimens and feasible to collect in human observational studies. Osborne and Monk (2013) conducted an early review of the literature, presented a theoretical basis for considering the role of the immune system in perinatal depression, and summarized available evidence regarding relevant inflammatory markers [8]. Here we present a brief review of the last five years of literature. We conducted a search using PubMed following the same search criteria as described in Osborne and Monk (2013), which was guided by the QUORUM and MOOSE checklists [18, 19] with three searches combined using the following terms as key words, along with closely matched MESH categories: (1) *inflammation, inflammatory, cytokine, immune, (2) depression, mood and (3) pregnancy, pregnant, antenatal, postnatal, postpartum, perinatal.* Results were limited to results since 2017. This search yielded 554 results which were downloaded for screening. After title and abstract screening, 453 articles were deemed irrelevant and excluded. The remaining 101 full texts were assessed for relevance to the present review. At this point, articles were included if they collected data from pregnant or postpartum women, included a measure of depression, included measurement of one or more inflammatory markers during pregnancy and/or the postpartum, and presented analyses of the association between inflammatory markers and either depressive symptoms or diagnosis of depression. Following this criteria, 39 studies were included in this review. Figure 1 presents a flow chart outlining the review process. We also conducted a secondary search for studies published 2013–2016 and identified a further 16 studies. Though not included in our synthesis, they are referred to when informative for this narrative review and discussion.

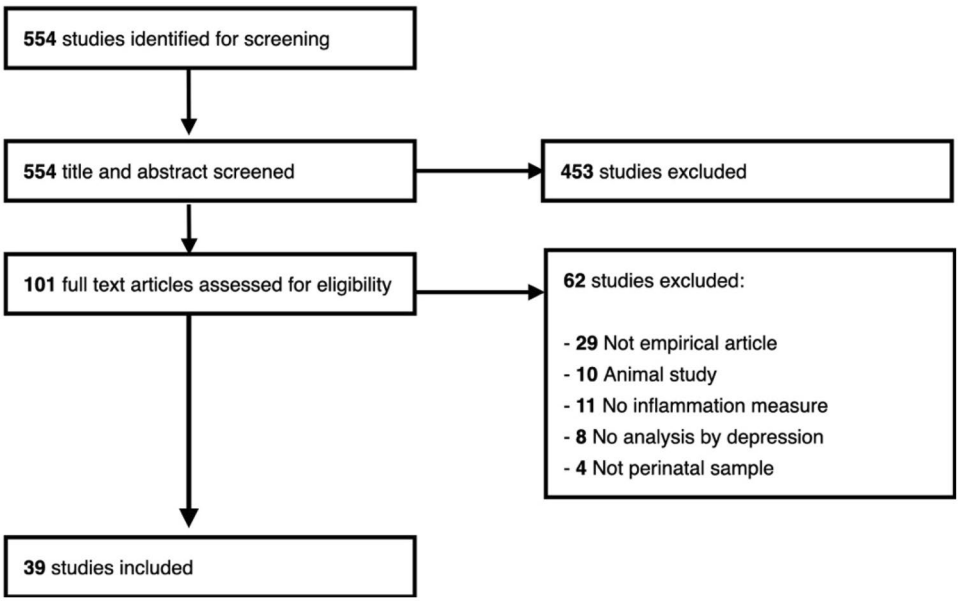


Fig. 1 Flow chart of search and study selection

Table 1 summarizes the methodologies and results from all studies included in this review. These studies are notably heterogeneous, taking divergent approaches to defining depression and measurement of different inflammatory markers at varying timepoints during pregnancy or the postpartum. Nevertheless, over the past decade sufficient data has emerged focusing on a core group of pro- and anti-inflammatory cytokines that there is now an opportunity to compare patterns of results across studies. To facilitate this, a generalization of findings organized by specific inflammatory markers is given in Table 2, selectively presenting markers for which data related to depression symptomatology or diagnosis was compared in at least two studies. Taken together, the sum of current evidence does not describe a straightforward immunological profile of perinatal depression yet suggests a possible role for immune functioning in this disorder's onset and maintenance.

Prenatal Inflammation and Perinatal Depression

The most commonly studied inflammatory markers in relation to depression are pro-inflammatory cytokines, notably IL-6, which was examined in 17 of the studies measuring prenatal inflammatory markers. In five of these studies, a significant positive association was observed between perinatal depressive symptoms and IL-6 levels during pregnancy [20–24]. In contrast, ten studies measured IL-6 during pregnancy but found no significant association with depression diagnosis or symptoms [25–35]. Two other studies did observe positive associations between prenatal IL-6 and depression but only in the context of other factors: comorbid anxiety [36] and experience of suboptimal care in own childhood [37], consistent with an association seen in an earlier study [38]. Another earlier study also observed an association only among those who also reported poor sleep efficiency [39], and a *negative* association between prenatal IL-6 and depressive symptoms was observed in another [40]. As outlined in Table 1, there is high heterogeneity between all studies which likely contributes to the inconsistencies in these findings, notably in terms of the populations studied, definition of depression and level of depression in samples, and analytic approach. Moreover, since those conducting subgroup or sensitivity analyses sometimes found evidence for important interaction effects between depression and other psychosocial factors on inflammation outcomes, associations at the population may not always be expected.

After IL-6, the next most frequently examined pro-inflammatory marker was TNF-α. Thirteen studies assessed TNF-α during pregnancy, only two of which reported a positive association with perinatal depression [24, 41]. One study reported higher TNF-α levels in women with depression who were non-responders to treatment and women with untreated depression compared to women with depression who were responsive to treatment [30], and two studies reported a positive association only in the context of higher maternal childhood maltreatment [25, 29]. Another study reported a *negative* association between prenatal TNF-α levels and depression [42]. The remaining eight studies found no association between TNF-α and depression [26, 27, 32–35, 43, 44]. Thirteen studies assessed CRP during pregnancy, with three reporting a positive association with depression [28, 33, 45]. One reported a positive association but only among women carrying male fetuses and not those carrying females [46]. Two studies reported a *negative* association between prenatal CRP levels and depressive symptoms [25, 47]; for one of these studies this was only true

Table 1 Summary of included studies with prenatal immunological measurement

Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
Achtyes et al. (2020) [53]	Postpartum women with significant symptoms of depression and suicidality, and healthy controls	147	6–12 weeks postpartum	EPDS	IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α	Elevated plasma IL-6 and IL-8 both increased the odds of PPD. Decrease in IL-2 increased risk for PPD. Modest evidence that increased TNF-α increased odds of PPD. No association with IL-10 and IL-1β
Bianciardi et al. (2021) [25]	Pregnant women with depression, healthy pregnant women, healthy controls	79	T2 (22–24 weeks gestation)	Clinical interview (DSM-5), EPDS	CRP, TNF α, IL-6	Increase in TNF α among those with elevated depression symptoms and history of trauma. Decreased CRP among those with depression but without trauma relative to controls
Bränn et al. (2017) [47]	Healthy pregnant women	291	Inflammation late pregnancy, mood postpartum	EPDS	92 inflammatory markers and methylation at CPG sites associated with genes corresponding to markers	STAM-BP (STAM-Binding Protein) was significantly lower among PPD group, after stringent adjustment for multiple comparisons. IL-10 was also lower
Bränn et al. (2020) [55]	Postpartum women with EPDS scores > = 13 and healthy controls	169	8–10 weeks postpartum	EPDS and MINI	70 inflammation-related proteins	5 inflammatory markers were higher in depressed group: TRANCE, HGF, IL-18, FGF-23, CXCL1
Bränn et al. (2022) [43]	Healthy pregnant and postpartum women and healthy controls	184	18 and 38 weeks gestation, delivery, 8 weeks postpartum	EPDS	IL-1β, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, M-CSF, VEGF-A	PPD groups had consistently lower VEGF-A. Lowest for Antenatal depression group and postpartum depression group compared to persistent depression
Bublitz et al. (2022) [59]	Pregnant women at risk for sleep apnea	98	Various across pregnancy	PHQ-9	Neutrophil to lymphocyte ratio (NLR)	Prenatal depression did not significantly predict change in NLR across gestation
Buglione-Corbett et al. (2018) [56]	Healthy pregnant women	63	28–34 weeks prenatal, 3 months & 6 months postpartum	EPDS	TNF-α, IL-6, IL-1-β, CRP	No association between EPDS scores and IL-6, IL-1-β, or CRP. Elevated TNF-α associated with lower EPDS scores

Table 1 (continued)

Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
Camacho-Arroyo et al. (2021) [50]	Healthy pregnant women	166	T3	HAMD, HAMA	Chemokines: [MCP-1 (CCL2), RANTES (CCL5), IP-10 (CXCL10), Eotaxin (CCL11), TARC (CCL17), MIP-1α (CCL3), MIP-1β (CCL4), MIG (CXCL9), MIP-3α (CCL20), ENA-78 (CXCL5), GROα (CXCL1), I-TAC (CXCL11) and IL-8 (CXCL8)]	P-10/CXCL10, I-TAC/CXCL11, and MIG/CXCL, IL-8/CXCL-8, MIP-1α/CCL3, MIP-1β/CCL4, and RANTES/CCL were higher in anxiety + depression group than controls. I-TAC/CXCL11, RANTES/CCL5, and MCP-1/CCL2 CCL11 displayed significant positive correlation with HAMD scores
Christian et al. (2018) [54]	Healthy pregnant women	69	7–10 weeks postpartum	CES-D	IL-6, TNF-α, IL-8	IL-6 and IL-8 correlated with CES-D symptoms among African American women but not White women. Total CES-D also correlate with IL-6 in African American women
Edvinsson et al. (2017) [52]	Pregnant women	217	35–39 weeks gestation	EPDS	74 inflammatory proteins	23 inflammatory markers differed between PPD and controls. Top 3 inflammatory factors down-regulated in women with prenatal depression were TNF related apoptosis-inducing ligand(TRAIL), macrophagecolony- stimulating factor1(CSF-1), and fractalkine(CX3CL1)
Finy and Christian (2018) [48]	Healthy pregnant women	214	Prenatal (Mean 17.7 weeks, range 5–31)	CES-D	IL-6, CRP	Depressive symptoms were positively correlated with IL-6 but not CRP
Freedman et al. (2021) [46]	Pregnant women	181	16 weeks gestation	CES-D	CRP	Interaction between CES-D and fetal sex on CRP: for women with male fetuses, CES-D positively related to CRP; no association among women with female fetuses
Gillespie et al. (2021) [51]	Non-Hispanic, Black, US-born healthy pregnant women	93	T3	CES-D	IL-6, IL-8, TNF-α, IL-1β,	NS

Table 1 (continued)

Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
Gustafsson et al. (2018) [24]	Healthy pregnant women	62	T3	CES-D	Latent variable of inflammation constructed including IL-6, TNF-α, MCP-1	Depressive symptoms were positively associated with inflammation
Jallo et al. (2021) [26]	Healthy pregnant women self-identifying as African American	72	14–17 weeks gestation	CES-D	IL-1β, TNF-α, IL-6, IL-8, and IL-12, IL-17, and IFN-γ	IL-8 positively correlated with depression. No association with other markers
Karlsson et al. (2017) [27]	Healthy pregnant women	150	Prenatal week 24	EPDS	48 different cytokines, chemokines, and growth factors	Positive correlation between Tth2-related cytokines (IL-5, IL-12, IL-9, IL-13) and EPDS score. The IFN-γ/IL-4 ratio and the concentration of IL-5 positively correlated with depressive symptoms. No association with IL-6 or TNF-α
Keane et al. (2021) [28]	Healthy nulliparous pregnant women	209	15 and 20 weeks gestation	EPDS	IFN-γ, TNF-α, IL-6, IL-18, IL-8, IP-10, MCP-1, SDF-1α, MIF, CRP	CRP levels significantly increased from week 15 to 20 in the high scoring EPDS group
Kleih et al. (2022) [29]	Healthy pregnant women	180	Early, mid, late gestation (mean 13, 21, 30 weeks)	CES-D	Composite score of IL-6 and TNF-α	NS
Lahti-Pulkkinen et al. (2020) [45]	Pregnant women at risk for preeclampsia	379	13,19, & 27 weeks gestation	CES-D	CRP	hsCRP levels higher in women with confirmed and probable depression before pregnancy. Remained significant adjusting for age, education, hypertension, diabetes; not significant after adjusting for BMI
Leff Gelman et al. (2019) [36]	Healthy pregnant women	298	T3	HDRS	Serum cytokines (IFN-γ,TNF-α, IL-6, IL-2, IL-5, IL- 13,IL-4, IL-10, IL-9, IL-17A, IL-17F, IL-21 and IL-22)	The anxiety + depression group showed positive correlations between IL-2, IL-6, and TNF-α cytokines and the depression score (HDRS), including the Th2-related IL-13, IL-10, and IL-9 mediators and Th17-associated IL-17A cyto-kines, respectively

Table 1 (continued)

Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
McCormack et al. (2021) [37]	Healthy pregnant women	187	T2 (24–27 weeks) T3 (34–37 weeks)	HAMD/CTQ/PBI	IL-6	Positive association between depression and IL-6 in T3 among women with early life caregiving adversity only
Miller et al. (2018) [30]	Pregnant women with symptoms of depression	85	12–20 weeks gestation	CES-D	IFN-γ, IL-13, IL-6, IL-8, TNF-α, CRP	Women with antenatal depression who were non-responders to treatment and women with untreated antenatal depressive symptoms had higher TNFα levels than women with antenatal depression but responsive to treatment
Miller et al. (2019) (1) [44]	Women with PPD randomized to transdermal estradiol, sertraline, or placebo for 8 weeks	35	Baseline 2–4 weeks postpartum, exit 8 weeks after treatment	HAMD—Atypical Depression Symptoms	CRP	NS
Miller et al. (2019) (2) [49]	Pregnant women presenting for scheduled cesarean delivery at term	117	At delivery 4–8 weeks postpartum	Inventory of Depressive Symptomatology-Self-Report	IL-1β, IFN-α, IFN-γ, TNF-α, IL-6, IL-8, IL-10, IL-12, IL-17A, IL-18, IL-23, and IL-33	No significant associations between any of the plasma cytokines and perinatal depression. Higher CSF IL-1β, IL-23, and IL-33 concentrations significantly associated with increased odds of perinatal depression
Min et al. (2022) [57]	Healthy postpartum women	226	6 weeks postpartum	EPDS (> 12 cutoff) STAI (> 15 cutoff)	Cell counts: Th1, Th2, Th17 Cytokines: IFN-g, IL-4, IL-7A	Th17 cells and IL-7A were positively correlated with EPDS score and STAI6 score and were higher in PPD and PPA cases compared to control
Nazzari et al. (2020) (1) [20]	Healthy pregnant women	104	Later gestation 12 week postpartum	EPDS STAI	IL-6, CRP	NS
Nazzari et al. (2020) (3) [31]	Healthy pregnant women	110	34–36 weeks gestation	EPDS STAI-S	IL-6	Prenatal Trp levels and Kyn/Trp ratio moderated association between IL-6 levels and depressive symptoms in pregnancy and postpartum
Nazzari et al. (2020) (2) [21]	Healthy pregnant women with vaginal deliveries	89	30–33 weeks gestation, delivery	EPDS STAI	IL-6 CRP	Higher depressive symptoms associated with higher IL-6 levels

Table 1 (continued)

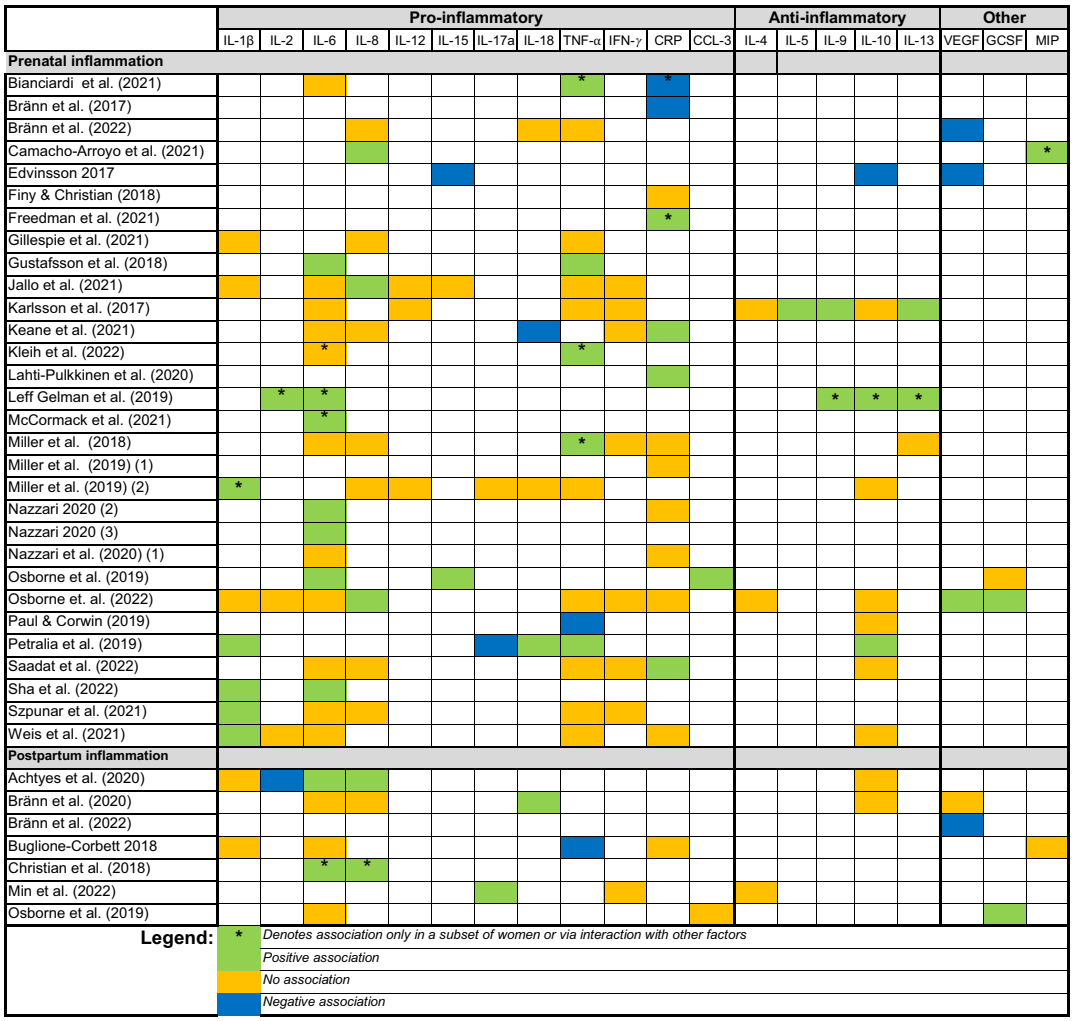
Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
Nishi et al. (2020) [84]	Healthy pregnant women	108	12–24 weeks gestation, T3	HAMD EPDS	IL-6, CRP	Neither E2 nor any PUFAs were associated with a change in inflammatory cytokines
Osborne et al. (2019) [22]	Healthy pregnant women	57	T1 (8–20 weeks), T2 (26 weeks, T3 (35 weeks), 6 and 24 weeks postpartum	BDI cutoff < = 9, STAI cutoff ≥ 35	IL-6, GCSF, IL-15, CCL3	Based on categorical BDI scores, IL-6, IL-15, GCSF, and CCL3 were significantly different across time, with IL-6, IL-15, and CCL3 higher in 3rd trimester in more depressed subjects
Osborne et al. (2020) [58]	Postpartum women with acute onset of severe PPD, and healthy controls	184	Depressed: day 61 postpartum Control: 31 days	SCID, EPDS	T-cell subtypes	Lack of increase in Th1 and Treg cells, in PPD women
Osborne et al. (2022) [32]	Healthy pregnant women	84	Early T3	BDI, STAI	IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, VEGF, EGF, MCP-1, IFN-γ, hsCRP	Women with history of depression who were symptom free in pregnancy showed increased prenatal IL-8, VEGF, and MCP-1 compared with healthy pregnant women
Paul and Corwin (2019) [42]	Healthy pregnant women	151	36 weeks gestation; Postpartum 1 and 2 weeks; 1, 2, 3, and 6 months	EPDS PSS	IL-6, TNF-a, IL-10	IL-6 and TNF-a associated with longer sleep duration and fewer depressive symptoms
Petralia et al. (2019) [41]	Preconception, Pregnant and postnatal women	62	Preconception, T1 and T3, early postpartum	BDI, HAMD, EPDS	Microarray transcript levels of 94 inflammation genes	PPD women relative to euthymic and always depressed women exhibit significant fluctuation in the levels in TNF superfamily and IL-8 among other cytokines and cytokine receptors
Saadat et al. (2022) [22]	Pregnant African American women	187	8–12 weeks gestation 13–29 weeks gestation	(CES-D cutoff > = 23	IFN-γ, IL-6, IL-8, IL-10, TNF-a, CRP	Higher CES-D scores were correlated with higher plasma CRP levels

Table 1 (continued)

Study ID	Population description	n	Time points	Measure of depression	Measures of inflammation	Main findings: Inflammation and depression
Sha et al. (2022) [23]	Healthy pregnant women	114	T1, T2, T3, postpartum	EPDS, SCID	IL-1β, IL-2, IL-6,IL-8, IL-10, and TNF. Other: tryptophan, serotonin, and kynurenine	IL-1β and IL-6 levels associated positively with severity of depressive symptoms across pregnancy and the postpartum. Odds of experiencing significant depressive symptoms increased with higher IL-1β and IL-6
Szpunar et al. (2021) [34]	Healthy pregnant veterans	18	T3, 6 weeks postpartum	EPDS, C-SSRS	IL-6, IL-8, IL-1β, IFN-γ, TNF-α	Elevated IL-1β was associated with suicidal thoughts during pregnancy
Weis et al. (2021) [35]	Pregnant women who are US active duty military beneficiaries (self or spouse active duty) randomized to supportive intervention or control	86	T1, T2, T3	EPDS	IL-2, IL-6, IL-10, IL-1 β, TNF- α, CRP	Positive association between depressive symptoms and IL-1β in control group. Women receiving intervention had longitudinally sustained lower TNF-/IL-10 ratios than the control group

Time points: T1: Trimester 1. T2: Trimester 2. T3: Trimester 3. **Depression measures:** EPDS: Edinburgh Postnatal Depression Scale. PHQ-9: Patient Health Questionnaire. CES-D: Center for Epidemiologic Studies – Depression scale. HAMD: Hamilton Depression Rating Scale. HAMA: Hamilton Anxiety Rating Scale. BDI: Beck's Depression Inventory. STAI: State Trait Anxiety Inventory. C-SSRS: Columbia Suicide Severity Rating Scale, SCID: Structured Clinical Interview for DSM-IV. PPD: Postpartum depression. **Inflammation markers:** IL-(x): Interleukin-(x), TNF-α: Tumor Necrosis Factor-alpha, CRP: C-Reactive Protein, hsCRP: high sensitivity C-reactive protein, M-CSF: macrophage colony stimulating factor, VEGF: Vascular endothelial growth factor, EGF: Epidermal growth factor, MCP-1: monocyte chemotactic protein-1, IFN-γ: Interferon-gamma, SDF-1α: Stromal cell derived factor-1, MIF: Macrophage migration inhibition factor

Table 2 Summary of associations between inflammatory markers and perinatal depression



for women with histories of sexual abuse [25]. The remaining seven studies reported no association between CRP and depression [20, 30–32, 35, 48, 49].

IL-8 was another frequently examined pro-inflammatory cytokine, which also shows mixed patterns of associations. In three of ten studies an overall positive association between IL-8 and depression was observed [26, 32, 50]. One earlier study reported a positive association but only among those reporting short sleep duration [39]. A further seven studies found no association between prenatal IL-8 and depression [28, 30, 33, 34, 43, 44, 51]. Prenatal IFN-γ was also relatively frequently examined, yet none of the seven studies assessing it in our review found any association between prenatal levels and depression [26–28, 30, 32–34]. Four studies observed positive associations overall between depression prenatal levels of IL-1β [23, 34, 35, 41], and a further study reported this positive association only when measured in CSF but not serum [44]. Other studies reported positive associations with less frequently examined cytokines, including IL-15 [22], IL-18 [41], and CCL-3 [22]. Consistent with their finding in relation to IL-6, Leff Gelman et al. (2019) also observed positive association between prenatal IL-2 and perinatal depression in the context of comorbid anxiety [36].

The most frequently examined anti-inflammatory cytokine was IL-10. In only one of nine studies examining this marker during pregnancy was an association found with depression [41]. In this case, IL-10 in the first trimester was upregulated in participants with postpartum onset of depression compared to euthymic participants, yet not in participants who were also depressed prior to pregnancy [41]. Leff

Gelman et al. (2019) found elevated levels of IL-10 in the 3rd trimester in women with significant anxiety symptoms alone, or comorbid anxiety and depression [36]. Edvinsson et al. (2017) found *negative* associations between IL-10 levels and depressive symptoms, which was the same pattern of results observed between depression and several other pro- and anti- inflammatory markers in the same study [52]. The other six studies that measured IL-10 in pregnancy found no association with perinatal depression [27, 32, 33, 35, 42, 44]. Two studies measured IL-4 in pregnancy and found no association with depression [27, 32]. Karlsson et al. (2017) measured several anti-inflammatory cytokines and reported positive associations between prenatal depression and concurrent IL-5, IL-9 and IL-13 levels, but no association with IL-4 or IL-10 [27]. Finally, Leff Gelman et al. (2019) also found elevated levels of IL-9 and IL-13 in the context of comorbid maternal depression and anxiety [36].

Postnatal Inflammation and Perinatal Depression

There is some data supporting an association between postpartum IL-6 levels and depression though findings are again mixed, with one out of the six studies reporting a positive association [53], one showing a positive association but only among those self-identifying with African American racial identity (and not White women) [54], and the remaining three failing to observe any association [22, 55, 56]. The only study measuring TNF-α in the postpartum reported a negative association with depression [56]. Postpartum IL-8 was associated with depression in one study [53]; a further study reported a positive association but only among self-identified African American women [54]. In terms of anti-inflammatory markers, neither of the studies that measured postpartum IL-10 reported an association with depression [53, 55], nor did the one measuring IL-4. [57]

A small number of studies have examined differences in immune cells in the context of postnatal depression. Osborne et al. (2020) measured T cell populations using flow cytometry in women with severe postpartum-onset depression and compared these to healthy postpartum controls and controls who were neither pregnant nor postpartum. They found that women with postpartum depression failed to mount the typical T-cell activation during the postpartum period that was seen in postpartum controls. T-helper memory cells were elevated in healthy postpartum women (compared with non-postpartum controls), yet lower than control groups in women with depression [58]. Another study measured helper T-cells in whole blood, along with their related cytokines, and found both elevated Th17 cells and the related cytokine IL-17A were positively correlated with both perinatal depression and anxiety [57]. A further study examined the neutrophil to lymphocyte ratio during pregnancy, an indicator of systemic inflammation. They found no association with prenatal depression, but women who reported sexual abuse history showed a greater increase in this ratio across pregnancy [59]. Together, these findings suggest immune cell dysregulation may be characteristic of perinatal depression, as has been observed in mood disorders outside pregnancy [60], yet this is an understudied area.

Dynamic and Interactive Effects Among Inflammatory Markers

The studies outlined above contribute to the identification of a potential neuroimmune profile of perinatal depression. However, given the marked inconsistency in results, it does not appear that levels of any individual pro- or anti-inflammatory marker is a useful predictor of perinatal depression, whether measured during pregnancy or in the postpartum: analyses taking into account the relative balance of pro- and anti-inflammatory markers may be more significant. Some recent studies have begun to address this limitation by examining overall immune system functioning and adaptation across this period, providing a broader characterization of the inflammatory system during the peripartum rather than a snapshot of one marker.

One approach to this is the use of a summary inflammation variable derived from measured levels of multiple inflammatory markers. Gustaffson et al. (2018) computed a latent variable indicated by levels of IL-6, TNF-α, and MCP-1 after a confirmatory factor analysis supported this approach. Inflammation in the 3rd trimester was positively associated with maternal prenatal depressive symptoms at 6 months postpartum [24]. Authors noted that the regulatory cytokine IL-10 also significantly loaded onto this general inflammation factor. Kleih et al. (2021) aggregated TNF-α and IL-6 and found no significant main effect for the association with depression, but did find a significant interaction between maternal exposure to childhood maltreatment and depressive symptoms with elevated inflammatory score [29]. Bränn et al. (2017) measured 92 different inflammation-related markers late in the 3rd trimester, and found 40 markers were lower among women who later showed elevated depressive symptoms at 6 weeks postpartum [47]. Following correction for multiple comparison, this difference remained significant for STAM-BP, AXIN-1, ADA, ST1A1 and IL-10. They also computed a summary inflammation variable comprised of 40 inflammatory markers; women with postnatal depression had lower median scores on this summary variable during pregnancy, suggesting there may be little predictive value of a single inflammatory marker [47]. Similarly, Edvinsson et al. (2017) in a partially overlapping sample, also found lower levels of 23 inflammatory markers among women with untreated antenatal depression and those using SSRIs during pregnancy, which authors suggest could reflect

a dysregulated shift towards a more anti-inflammatory state that occurs in healthy pregnancy [52].

Another approach for taking into account the complex interaction among inflammatory markers is to examine *relative* levels of different cytokines. A predominance of pro-inflammatory (Th1/Th17) cytokines over the levels of anti-inflammatory cytokines is thought to contribute to pathogenesis of depression. Supporting this, Corwin et al. (2015) found the IL-8/IL-10 ratio in the early postpartum to be associated with postpartum depression at 6 months [61]. During pregnancy, Karlsson et al. (2017) found that a higher IFN-γ/IL-4 ratio at 24 weeks gestation correlated positively with concurrent depressive symptoms [27]. A notable recent study employed a data-driven approach using a principal component analysis to integrate inflammatory markers as well as kynurenine metabolites, tryptophan, serotonin, and three derivative ratios [23]. The principal component approach demonstrated strong ability to predict depression: scores on the component variable in the 2nd trimester had a > 99% chance of being associated with depression severity in the 3rd trimester. The top contributors to this component variable were: TNF, Kynurenine/Tryptophan ratio (rKT), quinolinic acid (QUIN; a kynurenine pathway metabolite), kynurenine (KYN), QUIN/kynurenic acid ratio (rQK), IL-10, IL-6, and QUIN/picolinic acid ratio (rQP); they cumulatively explained > 90% of the variance in the principal component. Interestingly IL-6 and IL-10 were among the top inflammatory markers accounting for variance in this same study, and individually IL-6 and IL- 1β had the best performance among the individual biomarkers used to predict depressive symptoms. However, in combination with mechanistically relevant metabolites and derived ratios, the panel of factors demonstrated greater predictive power, suggesting its potential utility as a clinical marker of risk [23]. Osborne et al. (2019) conducted exploratory cluster analysis generating two groups with different balances of cytokine levels in the 3rd trimester – one group with relatively higher pro-inflammatory cytokine levels and one with lower levels. The two groups did not differ in terms of depression or anxiety symptoms but differed by race and BMI: the group with higher pro-inflammatory cytokines had fewer (self-identified) African American participants and more who self-identified as Hispanic, and also fewer subjects with BMI > 24 [22].

Since changes in immune system functioning are observed across healthy pregnancy [15], and perinatal depression varies in onset and trajectories of symptoms, differences in inflammation across pregnancy may reflect altered immune adaptation to pregnancy and contribute to risk for depression over time. The majority of studies outlined above are limited to cross-sectional analyses, but a small number have examined longitudinal data. Bränn et al. (2022) compared cytokine levels over the course of pregnancy among women with different trajectories of depressive symptoms peripartum. While women with prenatal or postnatal depression both had consistently lower levels of VEGF-A throughout the study time period (18 weeks gestation to 8 weeks postpartum) than controls, no difference in trajectory was observed: patterns of fluctuations in levels across the peripartum were not affected by depression [43]. Osborne et al. (2019) measured 23 cytokines at 5 different prenatal and postpartum time points and found a pro-inflammatory "burst" specifically in the 3rd trimester among women with both depressive and anxious symptoms. They also observed difference in the slope of change in cytokine concentration across pregnancy, with IL-6 and CCL3 decreasing from the 1st to 3rd trimester in less depressed women, yet the opposite pattern among more depressed women, as well as a lesser degree of decline in IL-15 among more depressed women [22]. Simpson et al. (2016) also reported no association between depressive symptoms and changes in inflammatory markers from pregnancy into the postpartum, though were limited by a small sample [62]. Szpunar et al. (2021) found depression symptom severity trended towards a positive association with larger increases in both IL-1β and TNF- α from pregnancy to postpartum, though this finding was not statistically significant.

Longitudinal studies are also necessary to determine whether inflammation measured at one time point is a potentially useful marker of risk for depression at later time points. This has been addressed by a relatively small number of studies with varying time points of assessment. As noted above, Brann et al. (2017) found 40 inflammatory markers measured in the 3rd trimester were lower among women who later showed elevated depressive symptoms at 6 weeks postpartum. Similarly, Gustaffson et al. (2018) demonstrated a composite inflammation variable in the 3rd trimester was positively associated with maternal prenatal depressive symptoms at 6 months postpartum [24]. Sha et al. (2022) reported that a principal component score derived from multiple inflammation markers in the 2nd trimester predicted 3rd trimester depression with high accuracy. Among studies examining individual inflammatory markers, McCormack et al. (2021) reported no association between 2nd trimester IL-6 and 3rd trimester depression levels. In a sample of women in treatment for postpartum MDD, Miller et al. (2019) observed no association between CRP levels in the postpartum with depression symptoms measured 4–8 weeks later. As the majority of studies have assessed inflammation and depression at concurrent time points, further studies are needed to determine whether alteration to the dynamic changes in immune system functioning that occur in healthy pregnancy are associated with depression onset or exacerbation, and whether inflammatory state measured at a single time point is predictive of future depression.

Neuro-immune Activity

If the peripartum period is a time of systemic immune modulation, is it also one of neuroimmune system modulation? And how might such changes affect mood outcomes? These questions are primarily addressed using animal models, and there are limited studies addressing this to date. The brain comprises its own immune cells that are in communication with the peripheral immune system through cytokines and chemokines crossing the blood–brain barrier [63]. Microglia, the brain-resident macrophages, play essential roles in normal physiology of the brain and behavioral outcomes [64] and are influenced by hormones [63, 65]. There is evidence for a transient reduction in microglia density during late pregnancy and into early and mid-postpartum period in several limbic brain regions, which was suggested to be due to attenuated microglial proliferation [66, 67]. In addition to microglia numbers, several studies indicate changes in the levels of cytokines. Specifically, a study found suppressed immune responses to lipopolysaccharide (LPS) stimulation during pregnancy indicated by low mRNA expression levels of IL-1β in the hippocampus and the medial prefrontal cortex [68]. Additionally, the study reported a reduction in mRNA IL-6 levels in the brain during pregnancy at baseline without diminishment in its response to LPS stimulation [68]. Others reported elevated expression levels of cytokines such as IL-16, IL-4, IL-10 immediately after birth in the hippocampus and prefrontal cortex [66, 67]. In humans, one study examined both plasma and cerebral spinal fluid (CSF) cytokines and found that only markers in CSF were associated with depression (IL-1β, IL-23 and IL-33); moreover, levels of cytokines in the different samples did not correlate with one another [44] suggesting differences in peripheral vs central inflammation. Together these findings suggest that there is a significant modulation of the neuroimmune system during the perinatal period, yet further research is needed to better understand its link to behavioral and mental health outcomes.

Social Determinants of Health

One of the reasons that immune system dysregulation is a compelling candidate mechanism underlying perinatal depression is the overlap in psychosocial risk factors for perinatal depression with those commonly associated with elevated inflammatory states. For example, early life stress is one of the most robust predictors of increased inflammation [69–72]. A meta-analysis indicated early life stress is associated with systemic inflammation (elevated IL-6, CRP, and TNF-α) in non-pregnant adults [73]. Experiencing early life stress also increases the risk for postpartum psychiatric illnesses [74] above and beyond the influence of sociodemographic status or existing psychopathology [75]. Experimental preclinical models also support this association: chronic stress and early life adversity increase the risk for abnormal postpartum behaviors and deficits in maternal care in rodents [76–78]. While this review has highlighted inconsistencies in findings regarding levels of inflammatory markers implicated in perinatal depression, there is evidence demonstrating that women with histories of childhood adversity *and* depression during pregnancy show higher levels of inflammation [25, 29, 37, 38]. Perhaps early adversity and related chronic stress affects immune system functioning, in line with an allostatic load model whereby chronic stress leads to vulnerability for dysregulated responses to further stress exposure and risk for illnesses including psychiatric ones [79, 80].

Other studies highlighted in this review found associations between depression and inflammation only among certain subgroups of women. Christian et al. (2018) found that among postpartum women, poorer sleep quality, parenting stress, perceived stress, and depressive symptoms were associated with elevated pro-inflammatory cytokine levels (IL-6, IL-8) – yet only among African American women and not White women [54]. Sleep quality was identified as a mediator and initiator linking stress with elevated inflammatory responding, consistent with previous findings demonstrating no difference in baseline IL-6 levels between Black and White women yet heightened response following a stressor exposure among Black women [81]. Gillespie et al. (2021) further found that among Black women in the 3rd trimester, an interaction between racial discrimination and chronic stress predicted IL-8 levels while the interaction of discrimination and acute stress predicted TNF-α and IL-1β levels [51]. Together, findings suggest potential racial differences in associations between psychosocial factors and inflammation at postpartum, yet this is an area in need of further investigation.

If the association between depression and inflammation is more pronounced among those also experiencing chronic stress and among underrepresented minority populations, this may partly explain the inconsistent findings between different cohort studies reviewed here, and the preponderance of null effects. Notably, the majority of studies specifically recruited healthy women with uncomplicated pregnancies, and many excluded those with common immune-related health conditions such as asthma. This could also contribute to null effects frequently seen since samples with stringent exclusion criteria may skew towards having a less inflammatory milieu than the general population. Furthermore, as is common in behavioral science, it is possible this field is affected by the "WEIRD problem"– an overrepresentation of wealthy, educated, industrialized, rich, and democratic participants, meaning results may not generalize to all populations [82]. Moreover, perinatal depression is a heterogeneous disorder with different psychosocial risk factors

associated with onset at different points during pregnancy, different symptom patterns, and therefore potentially resulting from divergent etiologies [83]. Altered inflammation among certain subsets of women suffering from perinatal depression may point to particular underlying or related pathology, yet there is insufficient granularity in the present literature to determine this.

Conclusions

There is substantial evidence implicating dysregulated immune activity in perinatal depression, yet little clarity regarding a consistent immune profile, especially based on analysis of circulating peripheral cytokines. Given the dynamic and interactive nature of immune activity, examination of relative levels of multiple inflammatory markers as well as longitudinal changes over this period are promising approaches for future research to continue to explore. The interaction between social determinants of health and chronic stress with immune activation is an important area of investigation: altered immune activity may be one mechanism by which these psychosocial factors contribute to increased risk for perinatal depression, and carefully accounting for these factors may produce more consistent results and thereby refine conceptual models of perinatal depression etiology. Clearly, studies actively recruiting diverse samples and those experiencing adversity are needed. Since peripheral immune markers are not necessarily directly related to central nervous system immune functioning, research investigating neuroimmune activity specifically would strengthen mechanistic understanding of how altered inflammation may affect the brain and contribute to the onset or exacerbation of depression in the perinatal period.

Declarations

Conflicts of Interests/Competing Interests The authors do not have existing conflict of interest.

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