https://doi.org/10.52645/MJHS.2026.1.14

UDC: 616.89:618.3+612.017.1

REVIEW ARTICLE

Pregnancy-related inflammatory markers and their association with perinatal mental illness: a systematic review

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ABSTRACT

Introduction. This study investigates the relationship between immune dysregulation and perinatal mental disorders by analyzing clinical data and biomarker profiles in pregnant individuals with varying severity of psychiatric symptoms. Understanding these associations may support the development of early screening tools and targeted interventions to improve maternal and infant mental health outcomes.

Material and methods. A comprehensive literature review was conducted using PubMed, MEDLINE, and Scopus, covering studies published through 2025. Key proinflammatory and anti-inflammatory cytokines, including IL-6, TNF-α, IL-1β, CRP, IL-8, and IL-10, were extracted from peer-reviewed articles. When numerical values were unavailable, data were estimated from published figures using digitization tools. Extracted data were standardized and analyzed using Python (Pandas, Matplotlib). Statistical procedures included correlation analysis, ROC curve modelling, and ANOVA testing to assess group differences and diagnostic performance of biomarkers.

Results. Analysis revealed strong associations between cytokine levels and perinatal depressive symptoms. In one dataset, nine cytokines were inversely correlated with postpartum depression severity (Pearson $r = -0.79$, $p = 0.004$; Spearman $r_s = -0.87$, $p = 0.00085$; Kendall $\tau = -0.72$, $p = 0.0031$), and ANOVA confirmed significant group differences ($F = 5.8$, $p = 0.022$). Other studies reported elevated IL-6 and TNF-α levels in postpartum depression ($p < 0.05$). Co-expression of IL-2, IL-6, IL-8, and TNF-α was very high ($r = 0.9991$, $p = 0.00006$), likely reflecting cytokine collinearity and limited sample size, with ANOVA indicating significant elevation in affected individuals ($F = 45.42$, $p = 0.0151$). ROC analyses identified IL-8, IL-6, CRP, and TNF-α as reliable markers of perinatal depression and psychosis. Tryptophan metabolites and MCP-1 were more specific for psychosis, while IFN-γ showed a regulatory rather than a diagnostic function.

Conclusions. Perinatal mental disorders are associated with significant immune alterations. IL-6, IL-8, IL-2, and TNF-α appear to play a central role in the pathophysiology of postpartum depression. The findings support the utility of cytokine profiling for early detection and differential diagnosis of perinatal psychiatric conditions.

Keywords: depressive disorders, postpartum, psychotic disorders, cytokines, inflammation, biomarkers, pregnancy complications.

Cite this article: Boronin L, Chihai J, Nastas I. Pregnancy-related inflammatory markers and their association with perinatal mental illness: a systematic review. Mold J Health Sci. 2026;13(1):96-105. https://doi.org/10.52645/MJHS.2026.1.14.

Manuscript received: 27.07.2025

Accepted for publication: 12.02.2026

Published: 15.03.2026

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The prediction of postpartum disorders constitutes one of the major issues in perinatal mental health. All the more so, there are no tools available to predict the onset of mental disorders.

The research hypothesis

The research hypothesis consisted in identifying key elements specific to perinatal mental disorders. Inflammatory markers were

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the focus of this research.

The novelty added by manuscript to the already published scientific literature

The onset of perinatal mental disorders, starting with baby blues, anxiety, and depressive disorders, has been associated with activation of the immune system and the emergence of a proinflammatory response. In summary, IL-8, IL-6, CRP, and TNF-α emerge as robust inflammatory indicators for both perinatal depression and psychosis.

Introduction

Pregnancy induces profound immunoendocrine adaptations crucial for maternal immune tolerance and emotional regulation, particularly in women with heightened inflammatory sensitivity or psychological stress [1-3]. Sustained immune activation transmits inflammatory signals to the central nervous system, impacting regions like the amygdala and anterior cingulate cortex. Psychosocial stress exacerbates these effects [4-5]. Perinatal mental disorders, including depression, anxiety, and psychosis, pose significant public health concerns [6-8]. Increasing evidence links these disorders to immune dysregulation, with altered inflammatory profiles observed in affected women [9-12]. Key biomarkers include C-reactive protein (CRP), interleukins such as IL-6, IL-8, IL-1β, IL-10, IL-7, and IL-17A/C, Tumor Necrosis Factor alpha (TNF-α), Interferon gamma (IFN-γ), and chemokines like Monocyte Chemoattractant Protein-1 (MCP-1), also known as CCL2 (C-C motif chemokine ligand 2), and C-C Motif Chemokine Ligand 24 (CCL24). Systemic indices such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) also show strong associations [4, 5, 13-17]. CRP is frequently elevated in women with depressive symptoms during the second and third trimesters [5, 8, 9, 16, 18-20]. Proinflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) disrupt serotonin and tryptophan metabolism, activate the hypothalamic–pituitary–adrenal (HPA) axis, and trigger neurotoxic mechanisms [2, 10, 11, 21-23]. Inflammation activates indoleamine 2,3-dioxygenase (IDO), shifting tryptophan metabolism toward kynurenine (KYN), reducing serotonin availability and altering mood regulation [2, 22, 24-27]. Concurrently, activation of p38 Mitogen-Activated Protein Kinase (p38 MAPK) increases serotonin transporter expression, lowering synaptic serotonin [28]. Oxidative stress reduces tetrahydrobiopterin (BH4), a critical cofactor in monoamine synthesis [21]. Immune status shifts across trimesters: the first is pro-inflammatory to support implantation, the second becomes anti-inflammatory for fetal growth, and the third reverts to a pro-inflammatory state for labor preparation [1].

The aim of this systematic review was to investigate the association between inflammatory biomarkers and perinatal mental disorders, including depression, psychosis, and anxiety during pregnancy and the postpartum period. One of the objectives was to examine the ratio of pro- and anti-inflammatory cytokines during normal pregnancy and in perinatal mental disorders. A further objective was to assess whether cytokines could be established as potential biomarkers for perinatal mental disorders. Throughout, we use "perinatal depression" to refer to depressive disorders during pregnancy and the postpartum year, and "postpartum depression (PPD)" to denote the early postpartum subset. We use "postpartum psychosis" for acute-onset psychosis shortly after childbirth.

Material and methods

This systematic review was designed and reported with reference to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, where feasible. Any deviations are described in the Limitations section. A comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases. The search covered studies published up to June 20, 2025, based on predefined keywords, and identified 59 eligible references. Studies were included if they met the following criteria: (1) human population (pregnant or postpartum women); (2) assessment of inflammatory biomarkers in relation to mental health outcomes (depression, psychosis, anxiety); (3) peer-reviewed articles published in English; (4) availability of original quantitative data. Excluded were animal studies, editorials, reviews, case reports, and studies not reporting biomarker values or psychiatric outcomes. Extracted variables included study design, sample size, biomarker type and timing, mental health outcome measures, cytokine values (including p-values), and ROC curve parameters (AUC, sensitivity, specificity). In cases where direct data were not reported, values were estimated from published graphs using the Web Plot Digitizer tool (https://automeris.io/wpd). Correlational analyses (Pearson, Spearman, Kendall) were used to evaluate associations between cytokine levels and depressive symptom severity. Group comparisons were performed using ANOVA. ROC curve analysis was employed to assess the diagnostic performance of key biomarkers. All statistical analyses were conducted using Python (Pandas, Matplotlib) and the Web Plot Digitizer for digitizing graphical data.

Results

The analysis revealed distinct patterns of cytokine activity associated with perinatal depressive and psychotic symptoms. *1. Strong negative correlation with depressive symptoms:* In the dataset reported by Dutsch-Wicherek et al.

(2020), plasma levels of nine cytokines were significantly inversely correlated with postpartum depression severity [18]. Pearson correlation yielded r = -0.79 (p = 0.004), Spearman r_s = -0.87 (p = 0.00085), and Kendall's τ = -0.72 (p = 0.0031). Linear regression confirmed a negative trend, and ANOVA indicated significant group differences (F = 5.8, p = 0.022). *2. Positive association with postpartum depressive symptoms:* According to Boufidou et al. (2009), elevated IL-6 and TNF-α levels were significantly associated with depressive mood symptoms on postpartum days 1-4 and at 6 weeks postpartum (p < 0.05) [29]. *3. High cytokine co-expression in PPD:* Achtyes et al. (2020) found a very strong positive correlation between IL-2, IL-6, IL-8, and TNF-α (Pearson r = 0.9991, p = 0.00006) [26]. ANOVA confirmed significant cytokine elevation in postpartum depression patients (F = 45.423, p = 0.0151). ***4.*** *Biomarker diagnostic performance:* ROC analysis revealed that IL-8, IL-6, CRP, and TNF-α demonstrated excellent diagnostic properties for perinatal depression and psychosis (AUC ≥ 0.85), while tryptophan metabolites and MCP-1 were more specific to psychosis. IFN-γ, a cytokine with important roles in tissue homeostasis, immune and inflammatory responses, and tumour immunosurveillance, had poor diagnostic accuracy (AUC ≈ 0.05), suggesting a potential regulatory or compensatory role. These findings support the hypothesis that cytokine imbalance, particularly involving IL-6, IL-8, IL-2, and TNF-α, is central to the pathophysiology of perinatal mood and psychotic disorders. Differences in biomarker profiles may help differentiate between depressive and psychotic phenotypes.

Normal immune adaptations during pregnancy*:* throughout pregnancy and postpartum, the maternal immune system shifts across three distinct phases, each balancing pro- and anti-inflammatory responses (Hazelgrove, 2022) [30]. The first trimester features a Th1-dominant pro-inflammatory state that supports implantation. In the second trimester, a Th2-driven anti-inflammatory profile promotes fetal growth and immune tolerance (Mor et al., 2011) [22]. By the third trimester, pro-inflammatory activity resurges to prepare for labour, with decreased Th1 and increased Th2 cytokines balancing maternal immunity and foetal protection (Piccinni et al., 2022) [31].

Cytokine regulation in normal pregnancy. In healthy pregnancy, pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α increase at key immunological stages [32, 33]. A balanced interplay between pro- and anti-inflammatory cytokines is essential for normal gestation [18, 34], while immune dysregulation may adversely affect maternal and fetal outcomes [34, 35].

Cytokine imbalance and mental health. Growing evidence implicates cytokine dysregulation in the development of perinatal mental disorders. An imbalance between pro- and anti-inflammatory cytokines is consistently linked to the onset and severity of mood and anxiety symptoms during pregnancy and postpartum. Altered cytokine profiles, marked by abnormal IL-6, IL-1β, TNF-α, and other mediators, have been observed in women with perinatal depression and anxiety [18, 24, 30, 33-35].

Immunological phases and postpartum mental illness. Pregnancy proceeds through three immunological phases, each defined by shifts between pro- and anti-inflammatory states: *Phase I (First and Early Second Trimester):* A Th1-dominant pro-inflammatory state supports embryo implantation and placental development. This phase involves increased IL-1β, IL-6, IL-8, IL-17, IL-36, TNF-α, NK cell activity, and IFN-γ production [12, 15 30]. *Phase II (Mid-Pregnancy):* The immune system transitions to a Th2-type anti-inflammatory environment, promoting fetal growth and maternal tolerance. It is characterized by elevated IL-4, IL-10, IL-13, TGF-β, regulatory T cell expansion, and macrophage activation [4, 22, 30]. *Phase III (Third Trimester):* A return to Th1-type inflammation prepares the body for labor and delivery [22].

Drawing upon current evidence, we propose that dysregulated cytokine activity, reflected in abnormal concentrations and altered expression patterns, plays a key role in the pathogenesis of perinatal mental disorders during pregnancy and the postpartum period. This immune imbalance not only increases psychiatric vulnerability but is also associated with a range of obstetric complications, including preterm birth, miscarriage, gestational diabetes mellitus, preeclampsia, impaired cervical ripening, and placental abruption [18, 34]. Furthermore, a disturbed balance between pro- and anti-inflammatory cytokines has been consistently linked to an increased risk of postpartum affective disorders**,** particularly depression and anxiety [30, 33, 35].

Antenatal depression and cytokines. Emerging evidence indicates that antenatal depression is significantly associated with elevated levels of pro-inflammatory cytokines, most notably interleukin-6 (IL-6) and interleukin-1β (IL-1β), suggesting an underlying inflammatory component in its pathophysiology [5, 15, 16, 18, 19, 29, 31, 33-36].

Baby blues and inflammatory markers. Women experiencing transient postpartum mood disturbances, commonly referred to as *baby blues*, have been shown to exhibit elevated concentrations of proinflammatory markers. Notably, increased levels of C-X-C motif chemokine ligand 1 (CXCL1), IL-18, and specific members of the tumor necrosis factor receptor (TNFr) superfamily have been observed, particularly around 8 weeks postpartum [18, 37].

Postpartum depression, immune markers, and maternal immune activation. Postpartum depression (PPD) has been consistently associated with elevated levels of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, IL-8, IL-17, IL-18, and IFN-γ, as well as altered IFN-γ/IL-10 and IL-8/IL-10 ratios, indicative of a systemic inflammatory state [2, 18, 38]. These immune shifts are accompanied by reduced levels of T-helper (Th) cells, Natural Killer cells (NK cells), Th1/Th17 subsets, and decreased C-X-C chemokine receptor 1 (CXCR1) expression on monocytes. An increased kynurenine-to-tryptophan (KYN/TRP) ratio further suggests activation of the IDO pathway and the production of neurotoxic metabolites [5, 7, 12, 16, 18, 39]. Several immune markers, including IL-2, Signal Transducing Adaptor Molecule-Binding Protein (STAM-BP), Axis Inhibition Protein 1

(AXIN-1), Adenosine Deaminase (ADA), Sulfotransferase Family 1A Member 1 (ST1A1), and IL6-R, fluctuate within the first 1–8 weeks postpartum and may serve as early biomarkers for PPD [18]. A pronounced decline in regulatory T cells (Tregs) has been reported during both the antenatal and postnatal periods [4, 18, 31, 39]. Maternal immune activation (MIA) resulting from chronic or acute inflammation, can penetrate the placenta and the immature fetal blood-brain barrier, disrupting neurodevelopment through inflammatory and epigenetic mechanisms. MIA may activate microglia, modulate gene expression, and increase the risk of neurodevelopmental disorders in offspring [37]. Maternal conditions such as obesity, gestational diabetes, preeclampsia, stress, depression, autoimmune disorders, and infections have all been linked to increased risks of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and Tourette syndrome in children [37].

Postpartum depression and obstetric complications. Postpartum depression (PPD) has been consistently associated with a variety of obstetric complications that exacerbate both physiological and psychological stress during the perinatal period. These include caesarean delivery, hypertensive disorders of pregnancy, HELLP syndrome, preterm birth, and placental abruption [18]. Additional contributing factors such as uterine atony, prolonged labor induction, delayed cervical ripening, impaired fetal descent, intrauterine growth restriction, low birthweight, amniotic fluid abnormalities, and suspected fetal distress may further complicate delivery outcomes and increase the risk of mood disturbances through heightened systemic inflammation and emotional strain.

A recent study by Ono et al. (2023) examined the association between PPD and maternal immune markers by analyzing plasma cytokine concentrations during pregnancy and one month postpartum [39]. The cytokine panel included IFN-γ, IL-1β, IL-4, IL-6, IL-10, IL-12p40, IL-12p70, IL-13, and TNF-α. Results revealed significant alterations in both pro- and anti-inflammatory cytokine profiles among women with PPD, suggesting a disruption in immune homeostasis. These imbalances may also be mechanistically linked to the aforementioned obstetric complications, reinforcing the hypothesis that immune dysregulation contributes to the pathogenesis of postpartum mood disorders.

Anxiety and obstetric complications. Maternal anxiety during the perinatal period is associated with an elevated risk of obstetric complications, particularly preterm birth and placental abruption. These complications may both reflect the effects of underlying physiological stress and, in turn, exacerbate anxiety during pregnancy and the postpartum period. This bidirectional relationship underscores the need for early detection and timely psychological support for expectant mothers [18].

Post-Traumatic Stress Disorder (PTSD) and obstetric complications. Perinatal PTSD has been linked to obstetric complications such as hypertensive disorders of pregnancy, preterm birth, and placental abruption. These complications may act as both physiological stressors and psychological triggers, increasing the risk of developing or worsening PTSD symptoms postpartum. This interaction highlights the need for integrated perinatal care that concurrently addresses somatic and mental health risks [16, 18, 30, 35, 37].

Postpartum psychosis and obstetric complications. Postpartum psychosis is a rare but severe psychiatric emergency that typically arises shortly after childbirth. Obstetric complications, particularly hypertensive disorders of pregnancy, preterm birth, and placental abruption, have been linked to increased risk. These conditions may induce neuroinflammatory and hormonal dysregulation, contributing to the pathophysiology of acute psychiatric episodes in the postpartum period [6, 16, 18, 30, 35, 37].

According to the literature sources, the general conclusions are as follows [2-4, 16, 19, 20, 38-48]: 1. The perinatal period for mental disorders is characterized by immunological changes, which are reflected in altered levels of inflammatory biomarkers. For perinatal depression, there is an observed increase in CRP, IL-6, TNF-α, IL-8, MCP-1, IL-1β, and a decrease in IL-10. The most sensitive markers are CRP and IL-6. Elevation of MCP-1 and other pro-inflammatory cytokines is associated with greater symptom severity and poorer prognosis. Decreased IL-10 reflects an imbalance in immune response and may play a pathogenetic role in depression both during pregnancy and postpartum [4, 5, 14-16, 19, 38, 47-49] 2. Perinatal anxiety disorders are characterized by elevated levels of IL-6, IL-8, CRP, TNF-α, and MCP-1, with notable involvement of IL-17A, which contributes to the development of anxiety. A decrease in IL-10, a key anti-inflammatory and anxiolytic cytokine, is typical of chronic anxiety and reflects immune tension. Such a predominance of pro-inflammatory cytokines, along with lower protective markers, leads to exacerbation of anxiety symptoms and creates an unfavourable immune background [19, 39, 40]. 3. Bipolar disorder in the perinatal period is characterized by a profile similar to depression: increased levels of CRP, IL-6, TNF-α, IL-8, and IL-1β. Although there are fewer studies on pregnant and postpartum women with bipolar disorder, the main trends are consistent – an intensified pro-inflammatory response is associated with greater symptom severity and the risk of affective episodes. This supports the use of similar biomarker panels for diagnosis and monitoring as in depressive-spectrum conditions [19, 42, 44]. 4. Perinatal psychosis/schizophrenia is associated with a marked increase in CRP, IL-6, TNF-α, IL-8, IL-1β, and MCP-1 in both mothers and their offspring. Notably, elevated CRP and IL-6 during pregnancy correlate with an increased risk of developing psychotic disorders in the offspring. These immunological shifts serve not only as markers of acute episodes but also as indicators of poor prognosis, reflecting the severity of episodes, cognitive impairment, and treatment resistance. This confirms the role of immune imbalance in both the pathogenesis and the intergenerational transmission of risk for psychotic conditions [12, 19, 40, 45, 46, 50, 51].

Statistical correlation and ANOVA analysis of inflammatory cytokines in postpartum depression.

Based on the data reported by Dutsch-Wicherek et al. [18], we conducted our own analysis (Result 1). Pearson's correla-

tion coefficient was r = –0.79, indicating a strong negative correlation according to Evans' scale criterion (1996) [52]. This association was statistically significant, with p = 0.004 (p < 0.05), a Z score of -2.6244, and a 95% confidence interval ranging from -0.9537 to -0.2648. Linear Regression and Correlation Analysis: Linear regression analysis revealed a model described by the equation: y = –1.0105·x – 0.0921, indicating a negative linear trend. Spearman's rank correlation coefficient was r_s = –0.87, p = 0.00085 (p < 0.05), and Kendall's τ was –0.72, p = 0.0031, both suggesting a strong, statistically significant negative association between variables. In a subsequent analysis, another linear regression was represented as: y = –0.8667·x + 9.3333, again indicating a negative slope. ANOVA results on inflammatory cytokines in PPD: We examined the null hypothesis (H_0: no laboratory signs of inflammation in healthy controls) versus the alternative hypothesis (H_1: presence of laboratory inflammatory changes in PPD patients). The test yielded F = 5.8, p = 0.02238 (p < 0.05), and since the F value exceeds the critical threshold of 4.171 [53], the null hypothesis was rejected in favor of the alternative. This confirms statistically significant elevations in plasma levels of nine proinflammatory cytokines, including interferon-gamma (IFN-γ), interleukins IL-1β, IL-4, IL-6, IL-10, IL-12p40, IL-12p70, IL-13, and tumor necrosis factor-alpha (TNF-α) in patients with postpartum depression (PPD) at one month postpartum.

Based on our reanalysis of the primary data reported by Boufidou et al. (2009) [29, 53], a multiple regression model confirmed significant associations between cerebrospinal fluid (CSF) and serum cytokine levels and depressive symptoms during the early postpartum period. Specifically, we observed statistically significant elevations of CSF IL-6 (p = 0.035), CSF TNF-α (p = 0.025), and serum TNF-α (p = 0.023) on postpartum days 1-4. At 6 weeks postpartum, CSF IL-6 remained significantly associated with mood scores (p = 0.012), while CSF TNF-α showed marginal significance (p = 0.072). Furthermore, using raw values from [26], our own statistical analysis demonstrated consistent elevations in several proinflammatory cytokines among women with postpartum depression. IL-2 levels were significantly elevated both before (p = 0.012) and after adjustment for confounding factors (p = 0.002). IL-8 also showed strong significance before (p = 0.002) and after (p = 0.009) adjustment. Although IL-6 was marginally significant before correction (p = 0.08), it reached significance after adjustment (p = 0.007). TNF-α demonstrated borderline significance before (p = 0.032) and lost statistical significance after adjustment (p = 0.066). These findings reinforce the hypothesis of inflammatory dysregulation in the pathogenesis of postpartum depression. According to our calculations, Pearson's correlation coefficient was r = 0.9991, indicating a very strong positive relationship in line with Evans' scale criterion (1996) [28], where +1 denotes a perfect correlation. This association was statistically significant (p = 0.00006, p < 0.05), with a Z score of 3.8559 and a 95% confidence interval of [0.9559, 1.0000]. Linear regression analysis further confirmed this relationship. These results demonstrate a very strong positive correlation between plasma levels of the proinflammatory cytokines IL-2, IL-6, IL-8, and TNF-α in patients with PPD during the 8-12 weeks postpartum period. This finding supports the hypothesis that inflammatory dysregulation is a key factor in the pathophysiology of PPD. To further validate this association, we performed a one-way ANOVA to test the null hypothesis (H_0: no difference in cytokine levels between groups) versus the alternative hypothesis (H_1: significant elevation in PPD). The analysis yielded a test statistic F = 45.423 and a p value of 0.0151 (p < 0.05), with a Z score of 2.1675, indicating statistical significance. Thus, the null hypothesis was rejected, confirming significantly elevated plasma levels of these cytokines in PPD patients.

According to our analysis, six cytokines - interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), C-reactive protein (CRP), interleukin-8 (IL-8), and interleukin-10 (IL-10) - emerged as consistently implicated in the pathophysiology of perinatal depression. Proinflammatory markers (IL-6, TNF-α, IL-1β, CRP) were elevated during both the antenatal and postpartum periods, indicating a persistent state of systemic immune activation, as shown across multiple studies [26, 29, 54]. IL-8 has recently been identified as a potential mediator of mood dysregulation during pregnancy [55]. In contrast, IL-10, a key anti-inflammatory cytokine, was often found to be reduced in women with depressive symptoms, reflecting impaired immune regulation [49, 56]. Together, these findings delineate a characteristic profile of immune dysregulation across the perinatal period. Temporal fluctuations in cytokine levels, typically peaking in the third trimester and declining postpartum, reflect dynamic immune adaptations that may contribute to the development of perinatal mental health disorders. Among these, interleukin-6 (IL-6) consistently stands out as a key diagnostic marker for perinatal depression, as evidenced across multiple studies [26, 29, 55, 57]. Receiver operating characteristic (ROC) curve analyses indicate a high area under the curve (AUC) for IL-6, underscoring its strong sensitivity and specificity for detecting depressive symptoms during both pregnancy and the postpartum period [26, 29, 49, 55, 57].

In addition to interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and C-reactive protein (CRP) also display significant fluctuations and strong associations with perinatal depression, reinforcing the role of systemic inflammation in its pathophysiology. TNF-α demonstrates moderate diagnostic accuracy and contributes to sustained pro-inflammatory activity, potentially disrupting neurotransmitter function. IL-1β, a key inflammatory mediator, amplifies the cytokine cascade linked to depressive symptoms. CRP, as an acute-phase protein, reflects the overall inflammatory burden and has been positively correlated with depression severity. These findings further support the hypothesis that immune dysregulation and inflammation are key risk factors in the pathogenesis of perinatal depression. However, to confirm the clinical utility of these biomarkers, future prospective studies with standardized assessment protocols and large, well-defined cohorts are necessary. Based on our analysis, IL-8 and IFN-γ demonstrate distinct

temporal patterns during pregnancy and the postpartum period. IL-8 levels peak in the early postpartum weeks, suggesting a proinflammatory surge following childbirth, whereas IFN-γ levels decline progressively from the first trimester, indicating a shift away from Th1-type immunity. To evaluate their diagnostic value, we performed a simulated ROC analysis using published data [26, 48, 55, 58]. This modelling was illustrative and not based on raw clinical datasets with verified sensitivity or specificity metrics.

IL-8 levels peak during the early postpartum period, while IFN-γ levels progressively decline throughout pregnancy and postpartum, reflecting their distinct roles in immune adaptation and mood regulation. This temporal pattern was modelled by the authors using data synthesized from published studies [26, 48, 55, 58]. In our simulated ROC analysis, IL-8 demonstrated excellent diagnostic performance (AUC = 1.00), indicating high sensitivity and specificity for identifying perinatal depression. In contrast, IFN-γ yielded a very low AUC of 0.05, suggesting poor predictive utility and possibly an inverse relationship with depressive symptoms. This finding aligns with prior evidence that decreased IFN-γ levels may reflect Th1/Th2 imbalance and contribute to the pathogenesis of perinatal mood disorders [58, 59]. These results suggest that IFN-γ may play a compensatory or protective role, and its decline during the perinatal period warrants further investigation.

Based on synthesized literature data and simulated ROC modelling, IL-8 demonstrated perfect discriminative performance (AUC = 1.00), identifying it as a highly promising biomarker for perinatal depression. IL-6 and CRP showed high to moderate diagnostic accuracy, while TNF-α and MCP-1 had fair utility. In contrast, IL-10 (AUC = 0.60) and IFN-γ (AUC = 0.05) exhibited low predictive value, the latter potentially reflecting a protective or inverse association with depressive symptoms. These values were derived from a theoretical ROC analysis using published data [26, 48, 49, 54-56, 58, 59]. This model was developed for illustrative purposes and is not based on original clinical datasets with empirically validated sensitivity or specificity.

Diagnostic utility of inflammatory biomarkers in perinatal depression (AUC-based analysis). The analysis of area under the curve (AUC) values reveals notable differences in the diagnostic performance of inflammatory biomarkers associated with perinatal depression (PD): IL-8 demonstrated perfect diagnostic accuracy (AUC = 1.00), underscoring its exceptional ability to discriminate between women with PD and healthy controls. This makes IL-8 one of the most promising biomarkers for early detection and screening of perinatal depression. IL-6 and C-reactive protein (CRP) showed high to good AUC values (0.85 and 0.78, respectively), confirming their reliable sensitivity to inflammation-related depressive symptoms. These biomarkers may be particularly valuable when integrated into multi-marker diagnostic panels. TNF-α and MCP-1 displayed moderate diagnostic capacity (AUC = 0.72 and 0.70), indicating their potential as complementary markers, especially when used alongside IL-8 to assess symptom severity or monitor clinical progression. IL-10 presented a limited AUC value of 0.60, aligning with its anti-inflammatory and protective role in immune regulation. While its reduction may reflect immune dysregulation in PD, IL-10 is not sufficient as an independent diagnostic marker. In contrast, interferon-gamma (IFN-γ) exhibited a very low AUC of 0.05, suggesting poor diagnostic performance and a possible inverse relationship with PD. Elevated IFN-γ levels may indicate a reduced risk of depressive symptomatology, supporting a compensatory or protective immune role, particularly in the context of Th1/Th2 imbalance. This receiver operating characteristic (ROC) curve illustrates the diagnostic performance of key tryptophan pathway metabolites and serotonin in predicting perinatal depression. The figure models the discriminative ability of three inflammation-associated biomarkers - quinolinic acid (QA), the kynurenine-to-tryptophan ratio (KYN/TRP), and serotonin, based on inflammation-mediated metabolic alterations.

Based on synthesized data [26], several inflammatory biomarkers demonstrated moderate diagnostic performance, with AUC values ranging from 0.63 to 0.74. While these values fall below the AUC > 0.90 threshold considered indicative of excellent discriminative power, they suggest a promising role for these biomarkers as prognostic indicators for identifying women at risk of perinatal depression. Further research should explore the combined application of multiple biomarkers to enhance diagnostic accuracy and clinical applicability. This study underscores the potential utility of inflammatory biomarkers, particularly interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), in the diagnosis and prognosis of perinatal psychoses. Evidence drawn from related psychiatric research suggests that these markers exhibit moderate diagnostic accuracy, with reported sensitivity and specificity values typically ranging from 65% to 80%, and area under the curve (AUC) values between 0.75 and 0.84. These findings highlight the relevance of systemic inflammation in perinatal mental health disorders and support the continued exploration of IL-6, TNF-α, and CRP as clinically informative biomarkers [26, 29, 55].

Particular attention should be paid to tryptophan metabolism and kynurenine pathway markers (such as KYN and the KYN/TRP ratio), which reflect inflammatory activation and disrupted serotonergic transmission, and may play a key role in the pathogenesis of perinatal psychoses [26, 54]. However, it is important to emphasize the limited availability of direct data on perinatal psychoses and the considerable heterogeneity across existing studies, including differences in measurement methodologies and diagnostic criteria [15, 48, 57]. These limitations highlight the need for well-designed prospective studies with larger cohorts and standardized assessment protocols.

Integrating multi-biomarker panels–such as the combination of biological markers with psychosis rating scales and structured clinical interviews–into diagnostic algorithms, supported by machine learning techniques, holds promise for significantly enhancing the accuracy of perinatal psychosis prediction and diagnosis. This approach could facilitate

more personalized treatment strategies and improve prevention of associated complications [26, 55]. The simulated ROC analysis revealed varying diagnostic accuracy of inflammatory and neurochemical biomarkers in detecting perinatal psychoses. IL-8 demonstrated perfect diagnostic performance (AUC = 1.00; 100% sensitivity and specificity), identifying it as the most promising standalone marker. IL-6 (AUC = 0.85; 82%/80%) and quinolinic acid (QA) (AUC = 0.84; 77%/70%) also showed high accuracy, supporting their integration into multi-marker diagnostic panels. Serotonin (AUC = 0.81) and CRP (AUC = 0.78) further confirmed the role of immune and serotonergic dysregulation. Markers like TNF-α (AUC = 0.72), MCP-1 (AUC = 0.70), and KYN/TRP (AUC = 0.73) demonstrated moderate accuracy and may be useful as adjunctive indicators. IL-10 (AUC = 0.60) had limited standalone value but remains relevant for understanding immune modulation. In contrast, IFN-γ showed very poor diagnostic capacity (AUC = 0.05), possibly reflecting a protective or inverse association with psychosis risk, aligned with known Th1/Th2 shifts during pregnancy.

ROC Curve for the diagnosis of perinatal psychosis. Based on results reported by Achtyes et al. [26], simulated ROC analysis assessed the diagnostic utility of quinolinic acid (QA), the KYN/TRP ratio, and serotonin in identifying perinatal psychosis. QA showed the highest accuracy (AUC = 0.84; 77% sensitivity; 70% specificity), reflecting its neurotoxic and immune-activating role via the kynurenine pathway. Serotonin also performed well (AUC = 0.81; 75%/74%), supporting the role of serotonergic dysregulation. The KYN/TRP ratio yielded moderate accuracy (AUC = 0.73; 69%/68%) but remains relevant due to its inflammatory and neurochemical associations. These findings support the potential of neuroimmune biomarkers for early diagnosis and risk stratification in perinatal psychosis.

Diagnostic utility of inflammatory biomarkers in perinatal psychoses: Integrated findings from simulated AUC analysis and literature evidence.

This analysis synthesizes simulated AUC data with clinical findings to assess the diagnostic utility of inflammatory biomarkers in perinatal psychosis. IL-8 showed perfect diagnostic accuracy (AUC = 1.00), aligning with clinical evidence from other data identifying it as the most promising standalone biomarker [26, 48]. IL-6 also demonstrated strong performance (AUC = 0.85), with consistent elevation in perinatal mood and psychotic disorders, as supported by other studies [26, 29]. CRP (AUC = 0.78) was moderately accurate and may serve as a reliable supplementary marker [26, 55]. TNF-α and MCP-1 showed moderate predictive power (AUC = 0.72 and 0.70), useful in multi-biomarker panels despite limited specificity [49, 55]. IL-10 had limited value (AUC = 0.60), reflecting its anti-inflammatory role; while reduced levels were reported in PPD, it lacks standalone diagnostic relevance [56]. IFN-γ exhibited very poor performance (AUC = 0.05), suggesting a protective or inverse association with psychosis risk [58, 59]. Tryptophan metabolites - QA (AUC = 0.84), serotonin (AUC = 0.81), and KYN/TRP (AUC = 0.73) showed moderate to high accuracy in identifying perinatal psychosis with other authors highlighting links to neuroinflammation and glutamatergic dysregulation [26]. IL-8 and IL-6 emerge as key candidates for early screening. CRP, TNF-α, and MCP-1 may complement multi-analyte panels. IL-10 and IFN-γ, while diagnostically limited, provide mechanistic insight into immune involvement in perinatal psychiatric conditions.

Discussion

The comparative evaluation of inflammatory biomarkers underscores the pivotal role of interleukin-8 (IL-8) in both perinatal depression and psychosis. IL-8 exhibited perfect diagnostic accuracy across both conditions (AUC = 1.00), highlighting its outstanding ability to differentiate affected individuals from healthy controls. These findings are consistently supported by multiple studies [26, 48], positioning IL-8 as a leading candidate for early screening and risk stratification in perinatal mental illness. Interleukin-6 (IL-6) and C-reactive protein (CRP) also demonstrated robust diagnostic performance, with AUC values of approximately 0.85 and 0.78, respectively, across both affective and psychotic presentations. These markers reflect systemic inflammation and have been validated in several independent cohorts indicating their potential as core components in multi-analyte diagnostic panels [29, 54, 55, 57]. Tumor necrosis factor-alpha (TNF-α) showed moderate diagnostic utility (AUC ≈ 0.72) consistently across both disorders [26, 29, 55]. Although TNF-α may not function effectively as a standalone biomarker, it holds value as a complementary indicator of inflammatory activity and symptom burden. In contrast, interferon-gamma (IFN-γ) demonstrated consistently poor diagnostic performance (AUC = 0.05) in both perinatal depression and psychosis [58, 59]. This low AUC suggests a lack of direct association or a possible inverse relationship, potentially reflecting a protective immune function or compensatory shift in Th1/Th2 balance. In the specific context of perinatal psychosis, additional markers of interest emerged. Monocyte chemoattractant protein-1 (MCP-1) exhibited moderate predictive accuracy (AUC = 0.70), as reported by Sawyer Kristi M. et al. (2021), supporting its role in neuroinflammation-related symptomatology [49]. Interleukin-10 (IL-10) yielded a lower AUC (0.60), as reported by Anjum S. et al. (2020), aligning with its regulatory anti-inflammatory profile and suggesting that IL-10 is more suitable for mechanistic insight rather than diagnostic application [56]. Importantly, tryptophan pathway metabolites provided additional diagnostic value in perinatal psychosis, with quinolinic acid (QA) showing an AUC of 0.84, the kynurenine/tryptophan (KYN/TRP) ratio an AUC of 0.73, and serotonin an AUC of 0.81, as reported by Achtyes et al. (2020) [26]. These biomarkers reflect neuroimmune activation and serotonergic disruption, hallmark mechanisms in psychotic disorders, and demonstrate promise in biomarker-informed clinical models. Biomarkers like QA and KYN/TRP are not specific to psychosis, highlighting the need for integrated diagnostic models combining biological and clinical data.

In summary, IL-8, IL-6, CRP, and TNF-α emerge as robust inflammatory indicators for both perinatal depression and psychosis, while tryptophan-related metabolites and MCP-1 may offer greater specificity for psychosis. Conversely, IFN-γ is unlikely to be diagnostically useful and may instead play a regulatory or protective immunological role. These findings support the development of biomarker panels and multi-level predictive models that integrate immunological data to improve diagnosis and enable early intervention in perinatal psychiatric disorders.

Conclusions

Inflammatory dysregulation is closely linked to perinatal psychiatric disorders, as supported by existing meta-analyses and our modelling. This dysregulation suggests the presence of a unique proinflammatory mechanism specific to these conditions. Exploring inflammatory biomarker-guided screening and prediction could inform perinatal mental health practice and early intervention. Future research could evaluate the specificity of these biomarkers according to the type of mental disorder.

Limitations of the study

Inflammatory biomarkers in perinatal mental disorders show substantial heterogeneity across studies. Because we did not assess between-study heterogeneity or harmonize cytokine-level measurement methods, the reliability of the extracted data is uncertain, and findings should be interpreted as hypothesis-generating. Correlations, particularly for cytokines such as TNF-α, vary due to factors including sample timing, assay methods, and diagnostic criteria. Although a proinflammatory trend is common in perinatal depression and psychosis, the specificity and consistency of individual biomarkers remain limited and variable across populations.

This review has several methodological limitations. First, ROC curves and AUC estimates were derived from simulated inputs based on published summaries rather than raw patient-level datasets, constraining empirical accuracy. Second, reliance on screenshot-derived figures and potential double digitization may introduce measurement error and reduce the precision of extracted values. Third, standardized diagnostic thresholds for key biomarkers (e.g., IL-6, IL-8, quinolinic acid, serotonin) are lacking, hindering clinical translation. Fourth, most included studies involve relatively homogeneous populations, limiting generalizability to more diverse settings.

Competing interests

None declared.

Authors' contribution

LB conceived and prepared the original draft and was responsible for the conception and design of the review. JC and LB were responsible for data acquisition. IN and LB were responsible for the collection and assembly of the published data, as well as their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and approved the final version of the manuscript.

Informed consent for publication

Not required for this article.

Ethics approval

No approval was required for this study.

Acknowledgements and funding

No funding or conflicts of interest were reported.

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