Journal of Affective Disorders 347 (2024) 635–644

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Prenatal mood and anxiety disorders and associated cytokine changes

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ARTICLE INFO

Keywords:
Pregnancy
Mood disorder
Anxiety disorder
SCID
IL-6
IL-10

ABSTRACT

Background: We examined whether women with prenatal mood and anxiety disorders would exhibit differential pro- and anti-inflammatory marker trajectories during the prenatal and postpartum periods compared to women without these disorders.

Methods: Approximately 179 pregnant women participated in a longitudinal study conducted in two urban areas. Blood samples for inflammatory markers were collected at six study visits. The Structured Clinical Interview for the DSM-IV (SCID) was administered to participants scoring above cutoffs on anxiety and depression. Pregnant women with SCID Axis I diagnoses of mood and/or anxiety disorders were compared to other participants on inflammatory markers. Multilevel modeling tested associations between SCID diagnoses and within-person interleukin (IL)6 and IL10 trajectories.

Results: Prenatal SCID diagnoses were associated with linear, quadratic and cubic change in IL6 from prenatal to postpartum timepoints. Women with a prenatal SCID diagnosis had steeper decreases and increases in IL6 during prenatal and postpartum periods. SCID diagnoses were associated with lower IL10 in mid-pregnancy to postpartum ($b = -0.078$, $SE = 0.019$; $p = .015$).

Limitations: Future studies would benefit from a larger sample size and a larger number of participants with SCID diagnoses. Future research should also examine whether different prenatal Axis 1 diagnoses are associated with different patterns of immune response in pregnancy.

Conclusions: Pregnant women with prenatal mood and anxiety disorders had greater fluctuations in IL6 across prenatal and postpartum periods and lower IL10 through pregnancy and postpartum. They may have different proinflammatory states that remain after birth without a reciprocal anti-inflammatory response.

1. Introduction

Perinatal mood and anxiety disorders include a range of mental health disorders that occur during pregnancy and up to one year postpartum. Compared to the general population, where the lifetime prevalence of mood disorders is approximately 21 % and the prevalence in any given year is about 10 %, perinatal mood and anxiety disorders (including unipolar depressive disorder, bipolar disorder, generalized anxiety disorder, panic disorder, and posttraumatic stress disorder) occur in 15 to 21 % of all U.S. pregnancies (Accortt and Wong, 2017; Gjerdingen and Yawn, 2007; Harvard Medical School, 2007; Reck et al., 2008; Wisner et al., 2013). The high co-morbidity and variable onset of perinatal depression and anxiety have led researchers and clinicians to advocate for revising the definition of perinatal depression, currently considered a single type of perinatal mood and anxiety disorders, to include both depression and anxiety disorders that occur during

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https://doi.org/10.1016/j.jad.2023.12.014
Received 20 April 2023; Received in revised form 11 November 2023; Accepted 2 December 2023
Available online 7 December 2023

pregnancy and/or the postpartum period (Meltzer-Brody and Rubinow, 2021). Perinatal mood and anxiety disorders are costly, impacting job productivity, effective parenting, child development, and healthcare expenses (Luca et al., 2020). They are also associated with adverse birth outcomes, such as shorter gestational age and lower birthweight, and poor postpartum health (Accortt et al., 2014; Dayan et al., 2006; Ding et al., 2014; Grigoriadis et al., 2018; Grote et al., 2010), but the physiological mechanisms that contribute to the relationship between perinatal mood and anxiety disorders, birth outcomes, and postpartum health are not well understood. The aim of this paper is to broaden our understanding of the ways in which perinatal mood and anxiety disorders may affect birth outcomes by examining the relationship between prenatal mood and anxiety disorders and immunological changes in pregnancy.

The immune system is one pathway through which prenatal mood and anxiety disorders may affect birth outcomes and postpartum health (Christian, 2012; Coussons-Read et al., 2003). Research on the psychoneuroimmunology of pregnancy indicates that when under stress, pregnant mothers are at higher risk of exhibiting neuroendocrine and immune dysfunction (Coussons-Read et al., 2007), which is associated with risk for adverse birth outcomes and poor postpartum health. Studies also suggest that mood and anxiety disorders in men and non-pregnant women are related to immune dysfunction (Dowlati et al., 2010; Hodes et al., 2016; Miller and Raison, 2016; O'Donovan et al., 2010; Saito et al., 2010). If women experience prenatal mood and anxiety disorders that result in immune dysfunction during pregnancy, they may experience negative birth outcomes and suboptimal postpartum health (Cappelletti et al., 2016).

It is well understood that pregnancy is a complex psychological and physical stressor. One of the physiological aspects of pregnancy that greatly contributes to its complexity is the systematic change that occurs in maternal immune activity during the prenatal and postnatal periods, as orchestrated by the maternal-placental-fetal unit (Mor et al., 2017). A healthy immune system functions by mobilizing a wide variety of cells that attack foreign bodies and repair injured tissue – a process known as the inflammatory response. Cells in the immune system communicate and interact through the use of proteins called cytokines, and they can either encourage the inflammatory response (pro-inflammatory) or discourage it (anti-inflammatory). Immune response has been described in previous research as being comprised of two main categories: T helper 1 (Th1) and T helper 2 (Th2). Th1 encourages inflammation and is characterized by pro-inflammatory cytokines (including IL6) and Th2 discourages inflammation and includes anti-inflammatory cytokines (such as IL10). The immune system is fundamental to a healthy pregnancy and to the return to baseline during the postpartum period. Early studies of immune response in pregnancy have suggested that while the normal immune system is characterized by a predominantly proinflammatory Th1 response, in pregnancy, the response is predominantly anti-inflammatory, garnering a stronger Th2 response (Chen et al., 2012; Kraus et al., 2012).

As the body of research on pregnancy has grown, however, our understanding of immunological patterns in pregnancy has become more nuanced, and the current conceptualization is that there is an optimal balance between Th1/Th2 and Th17/Treg that shifts as pregnancy progresses (Gelman et al., 2019; Larocca et al., 2008; Osborne et al., 2019a; Saito et al., 2011). Th17 (or T helper 17) is a group of cells that stimulate inflammation, including IL17A and IL22 while Treg (regulatory T cells) suppresses inflammation and, similar to Th2, includes IL10.

When pregnancy is initiated, a pro-inflammatory response is needed to facilitate implantation of the fertilized egg. As pregnancy continues, when more emphasis is placed on fetal development and growth, a stronger anti-inflammatory response is optimal (Mor et al., 2011; Mor et al., 2017; Mor and Cardenas, 2010). Later in pregnancy, a stronger pro-inflammatory response is once again warranted to prepare for labor and delivery. Consistent with this pattern, studies show that in the weeks immediately preceding labor and delivery, there is evidence that the proinflammatory response increases while the anti-inflammatory response decreases (Mor and Cardenas, 2010; Osborne et al., 2019a).

Supporting this conceptualization of a normal immunological pattern during pregnancy and postpartum, in a study by Ross et al. (2022) which utilized the same sample and timepoints, and similar methods as the current study, proinflammatory IL6 was shown to gradually increase from mid-pregnancy to labor and delivery and then decreased postpartum. Anti-inflammatory IL10 trended toward decreases from mid-pregnancy to labor and delivery and increased postpartum. This suggests that a prototypical immunomodulatory signature of pregnancy may be characterized by a complementary and counter-regulatory relationship between IL6 and IL10.

Adding to the evidence of shifts in immune response during pregnancy, several researchers have found that varying patterns of immune activation are dependent on the number of weeks gestation or the stage of pregnancy. Moreover, the postpartum immune system can exhibit these shifts for up to a full year after birth (Aghaeepour et al., 2017; Brann et al., 2019; Christian and Porter, 2014; Graham et al., 2017; Hedman et al., 2020; Kraus et al., 2012; Moore and Case, 2021; Stewart et al., 2007). Altered immune activity in the postpartum period, dubbed the "fourth trimester," (Paladine et al., 2019), is driven by recovery from labor and delivery, lactation, and sleep deprivation (Cunningham et al., 2014). This suggests that, beyond the immunological trajectories that emerge during pregnancy and shortly thereafter, there may be important immunological states that are adaptive while babies are breastfeeding and establishing the building blocks of their own immune systems. However, disruptions to these processes could affect postpartum recovery and return to pre-pregnancy baseline.

While pregnancy and the postpartum period are associated with unique immunological changes, psychological states also bring with them unique challenges to the immune system. There is a growing body of literature suggesting that mood and anxiety disorders are linked to specific immunological sequelae. Behaviors such as reduced physical activity, poor sleep quality (Okun et al., 2013), or smoking (which may worsen as a result of mood and anxiety disorders) could be driving changes in the immune system, or mood and anxiety disorders could directly affect activation of the hypothalamic-pituitary-adrenal and sympathetic-adreno-medullar axes which, in turn, have implications for immune function (Irwin and Cole, 2011; Sapolsky et al., 2000). In non-pregnant adults, anxiety and mood disorders are associated with altered inflammatory activity, particularly increased levels of pro-inflammatory IL6 (Dowlati et al., 2010; Haapakoski et al., 2015). In an extensive review of cytokine markers in depression, Hodes et al. (2016) reported that depression is most consistently associated with increases in IL6. Supporting this relationship, other studies have shown that injections of IL6 dampen the effect of anti-depressants, suggesting that IL6 plays a pivotal role in depressive symptoms (Sukoff Rizzo et al., 2012). The inflammatory patterns reported in the literature are not always the same and the causal direction is not fully established, but it is clear that a shift away from normal immune response is associated with mood disorders.

Consistent with research on mood disorders in the general population, mood disorders in pregnancy are also related to patterns of immune dysregulation (Accortt et al., 2023; Christian et al., 2009; Haeri et al., 2013; Osborne et al., 2018; Osborne et al., 2019b), and the concern arguably becomes greater because of the potential impact on both the mother and her unborn child. Assessing associations between anxiety and depressive symptoms during pregnancy and immune trajectories over time, one study reported higher inflammatory "spikes" in IL6 during the third trimester for women with greater anxiety and depression but not during the second trimester or 6 months postpartum (Osborne et al., 2019b). In a recent groundbreaking study, a cluster of biomarkers indicating unique patterns of neuronal signaling and immune dysregulation was identified in third-trimester pregnant women with perinatal mood and anxiety disorder symptoms (Accortt et al., 2023).

Significant associations between perinatal depression and

inflammation have been reported in several studies. For example, depression and stress have been associated with inflammation during pregnancy (Cassidy-Bushrow et al., 2012; Christian et al., 2009; Coussons-Read et al., 2007), and inflammation in the postpartum period has been associated with postpartum depression (e.g., Boufidou et al., 2009; Corwin and Pajer, 2008; Maes et al., 2000), although this relationship has been somewhat inconsistent (Okun et al., 2011; Skalkidou et al., 2009). In studies comparing pregnant women with major depressive disorder to pregnant women without a diagnosis, those with major depressive disorder exhibited higher IL6 and TNFα in the second and third trimesters (Haeri et al., 2013: Osborne et al., 2018) and higher anti-inflammatory IL10 in the third trimester (Osborne et al., 2018). There is also evidence that inflammatory markers may act as moderators of perinatal mood disorders. Accortt and colleagues found that prenatal vitamin D deficiency was associated with postpartum depression in a sample of 91 Black women, and this association was moderated by prenatal levels of IL6 (Accortt et al., 2016). Nonetheless, some experts feel that firm conclusions cannot be made about the role of inflammatory processes in perinatal depression at this point (Osborne and Monk, 2013). Firm conclusions are complicated by the use of a broad range of tools for mood assessment, different cutoff points, measurement of different cytokines, and racially and socioeconomically homogenous samples. Undeniably, the measurement of immune markers during pregnancy through the postpartum period is critical to understanding the impact of mood and anxiety disorders on perinatal immune function.

Although the literature suggests that prenatal mood and anxiety disorders are associated with altered inflammatory activity, we note that there are a number of important gaps in the research. First, previous findings have relied on single instances or average levels of immune activation with which to make conclusions about immunological patterns in pregnancy. The timing used for measurement of immune markers in pregnancy also varies in the literature (Brann et al., 2019; Curry et al., 2008; Graham et al., 2017; Hedman et al., 2020; Holmes et al., 2003; Reyes-Lagos et al., 2017; Ross et al., 2016). Second, few studies have focused on pregnant women with clinical diagnoses of anxiety and depression, relying on subclinical symptoms. Third, few studies have tested associations between prenatal mood and postpartum inflammation. If pregnancy is characterized by a dynamic immunomodulatory process that extends through the prenatal and postpartum periods, then multiple measures of immune activation in the prenatal and postpartum periods must be collected. Ross et al. (2022) report on trajectories of inflammatory markers in pregnancy and postpartum, contributing to our understanding of immunological changes in pregnancy.

In comparison to the study by Ross et al. (2022), we sought to contribute to a greater understanding of the effects of clinically diagnosed prenatal mood and anxiety disorders on the immune system during pregnancy by examining whether mood and anxiety disorders in pregnancy are associated with prenatal-to-postpartum changes in pro-inflammatory cytokine, IL6, and anti-inflammatory cytokine, IL10. In the current study, pregnant women with a SCID diagnosis of either a mood and/or anxiety disorder were compared to the other participants. We hypothesized that women with a prenatal diagnosis of a mood or anxiety disorder would exhibit significantly different trajectories of pro-inflammatory and anti-inflammatory markers during and after pregnancy.

2. Methods

2.1. Participants

The sample was comprised of 179 pregnant women in Healthy Babies Before Birth (HB3), a longitudinal study designed to test the impact of prenatal mood on birth outcomes and early infant development. Women receiving prenatal care at prenatal clinics and private practices located in Denver, Colorado (CO) and Los Angeles, California (CA) were included in the study if they were at least 18 years of age with a singleton intrauterine pregnancy <16 weeks gestation at the time of study recruitment. Spanish and English-speaking participants were recruited in CO while English-speaking participants were recruited in CA. The same sample was utilized in Ross et al. (2022).

Demographic data, including age, ethnicity, level of education, marital status, and maternal household income were collected. Sample characteristics are presented in Table 1. Women with a SCID diagnosis had significantly less education and were more likely to have a known obstetrical risk ($p < .05$) compared to women with no SCID diagnosis. Of the 179 participants, 21 women (12 %) received a diagnosis of Major Depressive Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Specific Phobia, Post-traumatic Stress Disorder, or Panic Disorder.

Participants were excluded if they were HIV positive, current smokers or engaged in substance abuse, taking medications known to affect the inflammatory response and/or had multiple gestations. A sample of 294 women enrolled in the study and completed baseline measures. Of those, 179 participants had complete SCID diagnostic data, covariate data, and inflammatory marker data at two or more time points.

2.2. Procedure

The study involved three prenatal visits and three visits after birth, with coordinated procedures and data collection across all study sites (identical to Ross et al., 2022). Each visit included completion of psychosocial assessments, collection of biological samples, and collection of medical records. Human subjects research approval was obtained from all applicable institutional review boards (Colorado Multiple Institutional Review Board (COMIRB), Cedars Sinai Medical Center Institutional Review Board, and University of California, Los Angeles

Table 1
Sample characteristics ($N = 179$).

Variable	Mn ± SD or % (N)			p
	Whole Sample (N = 179)	SCID diagnosis (N = 21)	No SCID diagnosis (N = 158)	
Site (Los Angeles)	63 % (113)	12 % (14)	88 % (99)	.876
Age (years)	31.0 ± 5.78	30.3 ± 6.79	30.2 ± 6.79	.922
Race/ethnicity				
Non-Hispanic White	46 % (82)	12 % (10)	88 % (72)	Ref
Hispanic	36 % (64)	10 % (6)	90 % (58)	.388
Other race/ethnicity	18 % (32)	15 % (5)	85 % (27)	.512
Per capita household income ($)	25,554 ± 24,391	16,299 ± 15,930	25,817 ± 24,763	.063
Education (years)	15.9 ± 3.19	14.1 ± 2.30	15.6 ± 3.43	.034
Gestational age at study entry (weeks)	14.0 ± 1.71	14.0 ± 1.74	13.9 ± 1.84	.735
Gestational age at birth (weeks)	39.3 ± 2.10	38.9 ± 2.14	39.4 ± 2.03	.285
Pre-pregnancy BMI (kg/m2)	26.3 ± 7.05	27.4 ± 8.73	26.3 ± 6.61	.443
Nulliparous	57 % (102)	10 % (10)	90 % (92)	.455
Child sex (female)	46 % (82)	9 % (7)	91 % (75)	.338
Any obstetric risk	44 % (79)	65 % (14)	40 % (63)	.027
Anxiety screener (OASIS)	3.15 ± 3.40	8.89 ± 4.31	2.35 ± 2.39	<.001
Depression screener (PHQ-9)	5.08 ± 3.80	10.8 ± 3.97	4.28 ± 3.03	<.001

Note: The Overall Anxiety Severity and Impairment Scale (OASIS) was used as the anxiety screening tool and the Patient Health Questionnaire (PHQ-9) was the depression screening tool in this study. Scores above clinical cut-offs triggered administration of the SCID.

Institutional Review Board, protocol 13-2325) and informed consent occurred in accordance with Human Subjects Research guidelines. In Los Angeles, participants were recruited for data collection at a major medical center mainly through direct patient contact at prenatal clinics, but also via brochures in OB/GYN practices and referral. In Denver, participants were recruited at a prenatal clinic affiliated with a major medical center serving mostly low-income women. They were identified at prenatal appointments, and if eligible, invited to participate in the study. Written informed consent was obtained from all participants who expressed interest.

Participants were evaluated at six time points: between 8 and 16 weeks gestation (T1), 20–26 weeks gestation (T2), 30–36 weeks gestation (T3), 4–8 weeks postpartum (P1), approximately 6 months postpartum (P2), and 1 year postpartum (P3). Visits were scheduled either in conjunction with regularly scheduled health care visits or at a time that was convenient for the participant. Extensively trained research staff conducted structured maternal psychosocial interviews and collected biological samples. Data were entered directly into REDCAP, a HIPAA compliant database (Harris et al., 2009).

2.3. Structured Clinical Interview for the DSM-IV (SCID)

The SCID, a semi-structured clinical interview, was used to diagnose Axis I disorders included in the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV) (First et al., 1996). The SCID is appropriate for general community samples and has validity and reliability in studies of pregnant women (Lobbestael et al., 2011). It was administered to all participants who scored above clinical cut-offs on screening tools for anxiety (Overall Anxiety Severity and Impairment Scale >7; Norman et al., 2006) and depression (Patient Health Questionnaire >10; Kroenke et al., 2001) at study outset. Interviews were completed by a trained Master's level clinician, and diagnoses were determined according to SCID protocol. At intake, 23 % of study participants ($n = 39$) were invited to complete a SCID interview. SCID diagnoses were recorded before T2. Because of the high comorbidity of perinatal mood and anxiety disorders and the emerging clinical view that these disorders should represent one inclusive diagnosis (Meltzer-Brody and Rubinow, 2021), participants were coded as either having a SCID diagnosis (1) or not (0).

2.4. Maternal health measures

2.4.1. Pre-pregnancy body mass index (BMI)

Participants reported their pre-pregnancy weight when they entered the study, and maternal height was measured at the initial study visit. Pre-pregnancy BMI (PreBMI; kg/m^2) was calculated by dividing the last pre-pregnancy weight (kg) by height squared (m^2). This measure of BMI was used as an indicator of adiposity rather than unspecified weight gain due to changes over pregnancy.

2.4.2. Gestational age (GA)

Medical charts were used to collect gestational age at study entry (Entry GA) and at delivery. Gestational age at delivery was estimated using participant reports of their last menstrual period and was then verified or adjusted by pelvic ultrasound, which was performed at each prenatal timepoint. For this sample, gestational age at delivery ranged from 22.14 to 42.14 weeks (M = 39.30, SD = 2.10).

2.4.3. Parity

Women were included if they were either pregnant with their first child (primiparous) or had previously given birth (multiparous). In this sample, 51 % of participants were primiparous and 49 % were multiparous.

2.4.4. Obstetric risk

Evidence of any obstetric complications during pregnancy was based on medical chart review and maternal self-report. Obstetric risk included evidence of any infection, anemia, preeclampsia, gestational hypertension or gestational diabetes. Approximately 44 % of the sample showed evidence of obstetrical risk.

2.4.5. Inflammatory markers

Blood samples were obtained by antecubital venipuncture by a trained phlebotomist or nurse at each assessment. Blood was collected into an EDTA-coated Vacutainer tube (BD Bioscience) and was centrifuged at 1300-1800 $\times g$ for 10–15 min immediately post-collection. Plasma was harvested and stored at —80C until assay. Cytokines were measured by electrochemoluminescent immunoassay on a MesoScale Discovery (MSD) instrument (SECTOR Imager 2400, Gathersburg, MD). Cytokines were assayed using a custom V-PLEX human plate [INFγ, IL10, IL6, IL8 and TNFα].[1] Participant samples were batched, and all plates were purchased from the same lot. Missing values were substituted by the lower limit of detection (LLD)/$\sqrt{2}$ (Ferguson et al., 2014). These analyses focused on pro-inflammatory IL6 and anti-inflammatory IL10 specifically. No significant effects were found for the remaining cytokines. Reliable values were obtained for both IL6 [average intra-assay CV (CV) = 5.21, LLD = 0.06 pg/mL] and IL10 (average CV = 8.40, LLD = 0.03 pg/mL). Distributions were positively skewed and were natural log (ln) transformed prior to analysis. Raw values for IL6 and IL10 are presented in Table 2.

2.5. Multilevel model formation

2.5.1. Covariates

Previous studies have found that sociodemographic, health, and pregnancy risk factors are related to varying levels of prenatal and postpartum inflammatory markers and there is evidence of racial/ethnic disparities in antenatal depression (e.g., Cappelletti et al., 2016; Christian et al., 2009; Christian and Porter, 2014; Coppack, 2001; Curry et al., 2008; Enninga et al., 2015; Finy and Christian, 2018; Gelman et al., 2019; Gillespie et al., 2016; Giurgescu et al., 2016; Keenan-Devlin et al., 2017; Miller et al., 2017; Mitchell et al., 2017; Mor et al., 2017; Mukherjee et al., 2016; Romero et al., 2001; Ross et al., 2019, 2022; Rowe et al., 2012). For this reason, PreBMI, Entry GA, age (at study entry, years), marital status (married or cohabiting or not), socioeconomic status (SES), race/ethnicity, parity (primiparous (0), multiparous (1)), child sex at birth (male (0), female (1)), obstetric risk (no risk (0), risk (1)), and SCID diagnosis were entered as covariates in the current analyses. Entry GA was included as a covariate to equate all participants with respect to gestation at baseline.

Identical to the measure used in Ross et al. (2022), SES was calculated from years of education and per capita household income. Household income was adjusted for cost of living between the two sites. Adjusted per capita household income was calculated by dividing adjusted household income by number of individuals in the household.

Table 2
Raw values for IL6 and IL10 at each assessment.

Assessment	Time (months)	IL6 (pg/mL)	IL10 (pg/mL)
T1	0.0 ± 0.0	0.697 ± 0.861	0.342 ± 0.255
T2	1.91 ± 0.495	0.683 ± 0.803	0.414 ± 0.655
T3	4.30 ± 0.556	0.836 ± 0.845	0.386 ± 0.548
P1	7.52 ± 0.609	0.975 ± 2.39	0.353 ± 0.773
P2	12.1 ± 0.640	1.05 ± 2.89	0.313 ± 0.368
P3	18.2 ± 0.702	1.00 ± 2.61	0.434 ± 0.231

[1] Cytokines were selected based on pilot assays performed using the V-Plex Proinflammatory Panel 1 Human Kit.

The SES index was calculated by standardizing education and adjusted per capita household income and taking the average of the standardized scores. Higher values indicate higher SES.

Race/ethnicity was dummy coded using two variables, one identifying Hispanic women (1) versus non-Hispanic women (0) (Race Hispanic); and the other identifying not Hispanic or White women (1) versus Hispanic or White women (0) (Race Other).

2.5.2. Analytic strategy

Two-level multilevel models were used to test associations between SCID diagnosis and IL6 and IL10 trajectories from mid-pregnancy to a year after birth, as shown in Eq. (1). All models were run using HLM 8.00 (Raudenbush et al., 2019). Within-person variables modeling time (months) were entered uncentered at Level 1. Linear (Time), quadratic ($Time^2$), and cubic ($Time^3$) trends in trajectories were modelled. Between-person variables (SCID diagnosis, all covariates) were grand centered and entered at Level 2. Estimated trajectories and intercepts were allowed to vary randomly. Models were estimated with robust standard errors and restricted maximum likelihood (REML). Cytokine levels and trajectories were not significantly affected by covariates.

Cross-level interaction terms (between Level 2 SCID diagnosis and Level 1 linear, quadratic or cubic trends in time) were probed by calculating cytokine trajectories for women with and without SCID diagnosis. Cytokine trajectories were calculated by subbing appropriate values into the multilevel model regression equations (Hox, 2010, p. 63–65). Missing data were imputed at Level 1. Listwise deletion was utilized if data were missing at Level 2.

3. Results

3.1. SCID Diagnosis and IL6 Trajectories

Multilevel models were run predicting IL6 trajectories from mid-pregnancy to one year after birth from SCID diagnosis and covariates. Fixed effects coefficients are presented in Table 3, and random effects are presented in Table 4. SCID diagnosis was not associated with IL6 at mid-pregnancy, $\beta_{011} = 0.050$, $SE = 0.070$, $p = .473$. However, SCID diagnosis interacted with linear trends, $\beta_{111} = -0.052$, $SE = 0.022$, $p = .017$, quadratic trends, $\beta_{211} = 0.008$, $SE = 0.004$, $p = .020$, and cubic trends, $\beta_{311} = -2.92 \times 10^{-4}$, $SE = 1.42 \times 10^{-4}$, $p = .041$, in time. IL6 trajectories for women with and without a SCID diagnosis are shown in Fig. 1. Women with a SCID diagnosis had greater increases and decreases in IL6 from mid-pregnancy to postpartum. Specifically, trajectories were characterized by greater increases in IL6 from mid-pregnancy to 6 months postpartum, and greater decreases in IL6 from 6 months postpartum to 12 months postpartum.

3.2. SCID Diagnosis and IL10 trajectories

Multilevel models were run predicting IL10 trajectories from mid-pregnancy to one-year after birth from SCID diagnosis and covariates. Fixed effects coefficients are presented in Table 3, and random effects are presented in Table 4. SCID diagnosis was associated with IL10 at mid-pregnancy, $\beta_{011} = -0.078$, $SE = 0.032$, $p = .015$, such that women with a SCID diagnosis had lower IL10 at mid-pregnancy. SCID diagnosis was not associated with linear, quadratic or cubic trends in IL10 from mid-pregnancy to a year post-birth, p's > 0.086, suggesting that women

$$[Inflammatory\ marker]_{ti} = \pi_{0i} + \pi_{1i} * (Time) + \pi_{2i} * (Time^2) + \pi_{3i} * (Time^3) + e_{ti}$$

$$\pi_{0i} = \beta_{00} + \beta_{01} * (PreBMI) + \beta_{02} * (Entry\ GA) + \beta_{03} * (Age) + \beta_{04} * (Marital\ Status) + \beta_{05} * (SES) + \beta_{06} * (Race\ Hispanic) + \beta_{07} * (Race\ Other) + \beta_{08} * (Parity) + \beta_{09} * (Child\ Sex) + \beta_{10} * (Obstetric\ Risk) + \beta_{11} * (SCID\ diagnosis) + r_{0i}$$

$$\pi_{1i} = \beta_{10} + \beta_{11} * (PreBMI) + \beta_{12} * (Entry\ GA) + \beta_{13} * (Age) + \beta_{14} * (Marital\ Status) + \beta_{15} * (SES) + \beta_{16} * (Race\ Hispanic) + \beta_{17} * (Race\ Other) + \beta_{18} * (Parity) + \beta_{19} * (Child\ Sex) + \beta_{110} * (Obstetric\ Risk) + \beta_{111} * (SCID\ diagnosis) + r_{0i}$$

$$\pi_{2i} = \beta_{20} + \beta_{21} * (PreBMI) + \beta_{22} * (Entry\ GA) + \beta_{23} * (Age) + \beta_{24} * (Marital\ Status) + \beta_{25} * (SES) + \beta_{26} * (Race\ Hispanic) + \beta_{27} * (Race\ Other) + \beta_{28} * (Parity) + \beta_{29} * (Child\ Sex) + \beta_{210} * (Obstetric\ Risk) + \beta_{211} * (SCID\ diagnosis) + r_{0i}$$

$$\pi_{3i} = \beta_{30} + \beta_{31} * (PreBMI) + \beta_{32} * (Entry\ GA) + \beta_{33} * (Age) + \beta_{34} * (Marital\ Status) + \beta_{35} * (SES) + \beta_{36} * (Race\ Hispanic) + \beta_{37} * (Race\ Other) + \beta_{38} * (Parity) + \beta_{39} * (Child\ Sex) + \beta_{310} * (Obstetric\ Risk) + \beta_{311} * (SCID\ diagnosis) + r_{0i}$$

Table 3
Fixed effects from multi-level models predicting IL10 and IL6 trajectories from pregnancy to one-year postpartum.

Outcome	Level	Fixed effect	b	SE	p
IL10	Intercept (π_0)	Intercept (β_{00})	0.314	0.019	<.001
		SCID Diagnosis (β_{011})	−0.078	0.032	.015
	Time slope (π_1)	Intercept (β_{10})	0.029	0.016	.076
		SCID Diagnosis (β_{111})	0.047	0.029	.109
	Time^2 slope (π_2)	Intercept (β_{20})	−0.007	0.003	.030
		SCID Diagnosis (β_{211})	−0.006	0.004	.108
	Time^3 slope (π_3)	Intercept (β_{30})	2.81×10^{-4}	1.30×10^{-4}	.032
		SCID Diagnosis (β_{311})	2.09×10^{-4}	1.21×10^{-4}	.086
IL6	Intercept (π_0)	Intercept (β_{00})	0.432	0.027	<.001
		SCID Diagnosis (β_{011})	0.050	0.070	.473
	Time slope (π_1)	Intercept (β_{10})	0.025	0.011	.022
		SCID Diagnosis (β_{111})	−0.053	0.022	.017
	Time^2 slope (π_2)	Intercept (β_{20})	−0.002	0.002	.190
		SCID Diagnosis (β_{211})	0.008	0.004	.020
	Time^3 slope (π_3)	Intercept (β_{30})	5.4×10^{-5}	6.1×10^{-5}	.383
		SCID Diagnosis (β_{311})	-2.92×10^{-4}	1.42×10^{-4}	.041

Table 4
Variance component estimates from multi-level models predicting inflammatory marker trajectories from pregnancy to one-year postpartum.

Outcome	Random effect	Standard deviation	p
IL10	Intercept (r_0)	0.074	<.001
	Time slope (r_1)	0.048	.003
	Time^2 slope (r_2)	0.009	.021
	Time^3 slope (r_3)	3.6×10^{-4}	.058
IL6	Intercept (r_0)	0.255	<.001
	Time slope (r_1)	0.032	<.001
	Time^2 slope (r_2)	0.004	.003
	Time^3 slope (r_3)	1.4×10^{-4}	.008

with a SCID diagnosis had lower IL10 from mid-pregnancy to one year postpartum.

4. Discussion

The purpose of this study was to examine whether a mood or anxiety diagnosis during pregnancy was associated with different trajectories of pro-inflammatory IL6 and anti-inflammatory IL10 from pregnancy to one year postpartum. Our results indicate that diagnosed prenatal mood and anxiety disorders are associated with different inflammatory marker trajectories, such that women with a SCID diagnosis had greater fluctuations in IL6 and significantly lower levels of IL10 over the pregnancy and postpartum period compared to women without these disorders. Whereas normal pregnancy involves an interplay of proinflammatory and anti-inflammatory processes, this suggests that prenatal mood and anxiety disorders may dysregulate normative pregnancy inflammatory processes, causing greater variability in proinflammatory response without the counter-regulation of anti-inflammatory pathways.

The findings presented here may reflect our focus on clinical diagnoses rather than subclinical symptoms as well as the utilization of a larger sample size and multilevel analytic approach to examining trajectories over time. We note that a similar study on the association between anxiety and depressive symptoms and changes in inflammatory markers over time yielded a slightly different pattern of results (Osborne et al., 2019b), such that anxiety and depressive symptoms were associated with increases in IL6 in the third trimester but not at other points in the perinatal period.

While outside the scope of the current study, future research should explore the potential impacts of diagnosed perinatal mood and anxiety disorders as well as symptoms of these conditions more broadly, and dysregulated maternal immune functioning on maternal and infant health. Research indicates that pregnant women with more depressive symptoms have higher levels of pro-inflammatory cytokines, and inflammation is associated with poor maternal and infant birth outcomes such as shorter gestation, miscarriage, and compromised fetal development (Christian et al., 2009; Christian, 2012). Recent evidence suggests that prenatal cytokine dysregulation is associated with higher incidence of autism spectrum disorder in offspring (Casey et al., 2022). Studies on obesity in pregnancy have shown that inflammation in pregnancy is associated with gestational hypertension and gestational diabetes (Christian and Porter, 2014). Research using animal models suggests that inflammation as a result of maternal obesity compromises the immunological, cognitive, and emotional development of offspring (Bilbo and Tsang, 2010). Adding to these findings, Christian (2015) notes that maternal immune dysregulation has been linked to the reactivation of latent viruses such as Epstein-Barr (EBV), and there is evidence to suggest that this reactivation may be associated with adverse maternal and infant outcomes such as shorter gestation and birth defects (e.g., Eskild et al., 2005). Furthermore, there is evidence to suggest that perinatal mood and anxiety disorders may hamper the development of healthy infant-caregiver attachment, affecting children's socioemotional adjustment (Erickson et al., 2019).

Pregnancy and the postpartum period are immunomodulatory events, with levels of IL6 and IL10 fluctuating during pregnancy and postpartum (Mor et al., 2017; Ross et al., 2022). Healthy pregnancy and recovery during the postpartum period may depend on adaptive regulation of these dynamic shifts in immune activity. Shifts that occur too early in pregnancy, for example, could increase risk for adverse outcomes such as preterm birth. Here, the immunomodulatory regulation in women with prenatal mood and anxiety disorders departed from the prototypical trajectory, suggesting that such regulation could be compromised. These findings add to our growing knowledge on prenatal mood and anxiety disorders and their relationship to the immune response.

Additional strengths in the methodology of the current study bolster our results on the association between prenatal mood and anxiety disorders and immunological markers. For instance, this is one of few studies that have provided the opportunity to compare diagnoses of anxiety and depression in pregnancy to women without diagnoses. A common limitation of studies in this field is that they do not involve diagnosed cases of prenatal mood and anxiety disorders. Structured diagnostic interviews, as opposed to screening tools, provide a higher level of confidence that women met criteria for the disorders and are at highest risk for developing a diagnosable mental health disorder (Accortt et al., 2021). This is a significant strength of the study. In addition, the measurement of pro- and anti-inflammatory immune markers allowed us to formulate a more nuanced picture of the pro- and anti-inflammatory immune response during healthy pregnancy in general, and in women with prenatal mood and anxiety disorders. Finally, this study is unique in that we collected data at multiple prenatal and postpartum timepoints through 12 months after birth, as compared to previous studies on mood and inflammation in pregnancy that focused on average levels, inflammatory markers at single time points, or markers within a more truncated perinatal period (Cassidy-Bushrow et al., 2012; Christian et al., 2009; Haeri et al., 2013; Osborne et al., 2018). All of these strengths enabled us to better capture the dynamic shifts of inflammatory activity over time that have been found to occur at various stages in pregnancy (Mor et al., 2017; Ross et al., 2022).

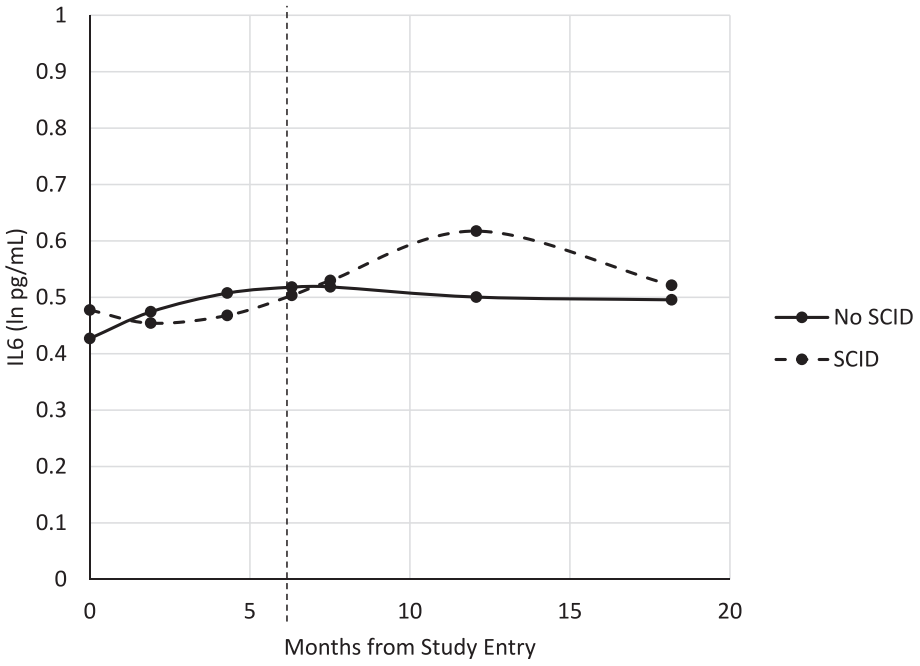

Fig. 1. IL6 trajectories for women with and without a prenatal SCID diagnosis. Women with a prenatal SCID diagnosis had greater fluctuations in IL6, with later increases in IL6 during pregnancy, and increasing IL6 up to 6 months postpartum. In contrast, women without a prenatal SCID diagnosis had smaller fluctuations in IL6.

4.1. Limitations

Nonetheless, we acknowledge limitations in the current study. Research with even larger samples and a correspondingly larger number of participants with SCID diagnoses is needed, as well as a mixed methods approach that includes both dichotomous and continuous screening data. Future studies would also benefit from greater representativeness in the sample. While there was ethnic diversity in this study, SES diversity was limited. One other aspect to consider in the current study is that we grouped together all prenatal anxiety or depressive disorders (Axis 1 in the DSM-IV). Although this is consistent with previous studies, future research should examine whether each of these diagnoses is associated with a different pattern of immune response in pregnancy. We acknowledge, however, that it is often difficult to gather a large enough sample size of pregnant women with a SCID diagnosis.

Given the complexity of the immunomodulatory processes studied in this paper, it would be helpful to explore additional immune markers in order to formulate a clearer picture of healthy and at-risk pregnancy. For instance, Th17 cells are believed to be highly regulated by IL6, and they are implicated in the development of several autoimmune disorders (Osborne et al., 2019a; Saito et al., 2010; Tesmer et al., 2008). It may be that Th17 mediates the role of IL6 in pregnancy and birth outcomes. Studies also suggest that Th17 cells play a significant role in mood disorders, making Th17 a strong choice for future research. New evidence of a cluster of biomarkers in the plasma of pregnant women suggests that it may be possible to develop a diagnostic panel (blood test) that identifies women at risk which could lead to earlier diagnosis and treatment of perinatal mood and anxiety disorders (Accortt et al., 2023).

The findings reported in this paper are consistent with previous literature suggesting that perinatal mood and anxiety disorders are associated with disrupted prenatal to postpartum inflammatory activity, and this study was able to examine immune response over time, however, the directionality of this relationship warrants continued study. For instance, it may be that prenatal mood and anxiety disorders are caused by inflammation. Mentioned previously, injections of IL6 have been shown to dampen the effect of anti-depressants, a finding that supports the influence of inflammation on depressive symptoms (Dowlati et al., 2010; Haapakoski et al., 2015; Sukoff Rizzo et al., 2012). Subsequent studies should also focus on establishing a causal direction between prenatal mood and anxiety disorders, immune activity, and birth outcomes and examine changes over time through structural equation modeling and other techniques rather than single time points or average levels if we are to make progress in understanding the role of the immune system in pregnancy. Furthermore, a more extensive examination of the impact of maternal immune response on offspring would be a valuable extension of research in this area.

In conclusion, the findings presented here contribute to the growing body of evidence suggesting that prenatal mood and anxiety disorders could be associated with perturbations in inflammatory regulation during pregnancy and the postpartum period. They represent an addition to our knowledge of the complex interplay between psychological and immunological mechanisms in the context of pregnancy. These mechanisms have implications for maternal health and may also impact infant growth and development.

Source of funding

The Healthy Babies Before Birth (HB3) Study was supported by funding from NIH (R01 HD073491: MPI M. Coussons-Read & C. Dunkel Schetter). REDCap is supported by the Colorado Clinical and Translational Sciences Institute (CCTSI) with the Development and Informatics Service Center (DISC) grant support [NIH/NCRR Colorado CTSI Grant Number UL1 RR025780].

CRediT authorship contribution statement

Roberta A. Mancuso: Conceptualization, Supervision, Project administration, Methodology, Visualization, Writing – original draft. **Kharah M. Ross:** Conceptualization, Visualization, Writing – original draft, Methodology, Formal analysis. **Eynav Accortt:** Writing – review & editing, Methodology, Supervision. **Mary Coussons-Read:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing, Methodology, Resources. **Michele L. Okun:**

Data curation, Methodology, Formal analysis. **Jessica Irwin:** Investigation. **Judith Carroll:** Formal analysis, Writing – review & editing. **Calvin J. Hobel:** Conceptualization, Supervision, Investigation, Resources. **Christine Dunkel Schetter:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing, Methodology, Resources.

Declaration of competing interest

Eight of the nine authors of this manuscript declare no conflict of interest. One author declares a potential personal, financial, and employment conflict of interest.

Acknowledgements

The authors thank the staff and the participants, especially Susan Jackman, RN, MA, coordinator of the Cedars Sinai Health Center site, and Rachel Holm, MS, coordinator of the Denver Health site.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.12.014.

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