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Psychiatric Symptoms and Proinflammatory Cytokines in Pregnancy

Emma Robertson Blackmore, PhD, **Jan A Moynihan, PhD**, **David R Rubinow, MD**, **Eva K Pressman, MD**, **Michelle Gilchrist, BA**, and **Thomas G O'Connor, PhD**
Departments of Psychiatry (ERB, JAM, MG, TO'C) and Obstetrics and Gynecology (EKP), University of Rochester Medical Center, Rochester, NY; and Department of Psychiatry, University of North Carolina, Chapel Hill (DRR)

Abstract

Objective—Clinical studies suggest that psychiatric symptoms, particularly depression, anxiety and trauma, may be associated with inflammation, as indexed by proinflammatory cytokines. Such a link may be especially significant in pregnancy, and may shed additional light on the etiology of perinatal mood disorders.

Methods—We prospectively followed 145 women selected from a community obstetric clinic serving a primarily low-income, high psychosocial risk population. Women without evidence of medical high-risk pregnancies were screened (including psychiatric and trauma histories) and then assessed in detail (e.g. mood symptoms) at approximately 18 and 32 weeks gestation. Blood was drawn to measure key proinflammatory markers, interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Data on pregnancy and obstetric outcome were derived from medical records.

Results—There was considerable stability of cytokine levels within individuals and a significant mean increase across pregnancy observed for IL-6 ($p<.001$) and TNF-α ($p<.001$). History of trauma was associated with significantly elevated TNF-α ($F(1.135)=4.43$, $p<.05$), controlling for psychosocial and obstetric covariates. In contrast, elevated measures of depression and anxiety were unrelated to proinflammatory cytokines ($p>.10$). Exploratory analyses indicated that neither psychiatric symptoms nor proinflammatory cytokines predicted birthweight, gestational age, or obstetric complications.

Conclusions—These findings suggest that antecedent trauma may be associated with persistently elevated TNF- α levels during pregnancy. No evidence was found that a generalized proinflammatory state was associated with symptoms of depression or anxiety in pregnant women.

Keywords

pregnancy; depression; trauma; proinflammatory cytokines

Introduction

Psychiatric disorders during pregnancy represent a major public health concern because of their prevalence and persistence into the postpartum period (1, 2). Public health and clinical concerns about prenatal psychiatric disturbance are most acute for minority women of lower socioeconomic status who exhibit increased prevalence of depressive symptoms (3–6). For

Address correspondence to: Emma Robertson Blackmore, PhD, BOX PSYCH 4-9200, University of Rochester Medical Center, 300 Crittenden Boulevard, Rochester NY 14642-8409. emma_robertsonblackmore@urmc.rochester.edu, (ph): 585 273 4484, (fax) 585 276 2065.

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example, a large-scale study of low income minority pregnant women reported that 29.3% (7) had experienced a traumatic event; another study of a similar population reported rates of post traumatic stress disorder (PTSD) to be 7.7% (8). Markedly elevated rates of co-morbid depression (42.2% and 66.7%) and anxiety disorders (any anxiety disorder 35.1%, panic disorder 36.4%) were found in studies by Loveland Cook et al (8) and Smith et al. (7), respectively.

The pathophysiology underlying mood changes throughout the perinatal period is not fully understood. Potential mechanisms currently being investigated include genetic vulnerability (9), disruption of the HPA axis (10, 11), sensitivity to changes in levels of steroid hormones (11, 12) and other markers of stress including sleep disruption (13, 14). In the current paper, we consider the hypothesis that prenatal mood disorders may be associated with cytokines (low molecular weight, circulating messenger proteins) that often promote inflammation (i.e., proinflammatory cytokines), specifically Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-6.

Although IL-6 and TNF-α are both involved in immune responses, hematopoeisis, and inflammation, they are distinct proteins with their own characteristic functional properties (15). These cytokines are secreted by monocytes/macrophages within the immune system and other organs. However, TNF-α can be produced by some T helper, Th 1cells, whereas IL-6 is produced by Th 2 cells. Further, IL-6 is, notably, secreted by adipocytes and endothelial cells. Although both IL-6 and TNF-α are important components of acute phase responses to a variety of challenges, there are a number of studies that report low correlations between these two cytokines (16–19).

A growing body of literature suggests that proinflammatory cytokines may be causally associated with psychiatric symptoms (20, 21). Evidence for this derives from several sources involving non-pregnant samples. First, exposure to psychosocial stressors, including marital difficulties and childhood maltreatment, is associated with inflammation and proinflammatory cytokine production (22–24). Second, illnesses characterized by chronic inflammatory responses are also associated with depression (25). Third, the administration of cytokines such as IFN-α to treat infectious diseases or cancer often results in patients exhibiting ‘sickness behaviors’ analogous to depressive symptoms; these symptoms ceased when treatment was stopped, and the symptoms were attenuated with antidepressant treatment (26–28). A recent meta-analysis found that compared to control subjects, patients with major depression had significantly higher concentrations of IL-6 and TNF-α (29); associations with other cytokines were not significant. Studies of cytokines and anxiety symptoms are fewer and focus particularly on PTSD (30, 31), but also provide robust evidence that compared to controls, subjects with PTSD have significantly increased levels of serum IL-6 (32–34) and TNF-α (33, 34).

It is not yet clear whether the link between psychiatric symptoms and proinflammatory cytokines reported outside of the perinatal period exists during pregnancy, or how this may help to explain prenatal mood disorders. Pregnancy is characterized by substantial alterations in endocrine and immune measures with obvious functional importance (35), and these pregnancy-related changes may disguise or confound a link with psychiatric symptoms. Available data indicating such relationships are limited, but suggestive. Coussons-Read et al (36,37) reported a significant association between elevated psychosocial stress scores and higher levels of IL-6 and TNF-α measured in the first and third trimesters. Christian et al (38) did not find a significant association between perceived stress and either IL-6 or TNF-α at 15 weeks gestation, but did report that depressive symptoms were significantly and positively associated with IL-6 and marginally with TNF-α. More work is clearly needed to determine if a link exists, whether or not it is evident

throughout pregnancy, and which symptom patterns are most closely associated with cytokine production. Accordingly, the central aim of this short-term longitudinal study is to investigate the link between psychiatric symptoms and proinflammatory cytokines in a sample of pregnant women using a broad index of psychiatric symptoms.

Considerable evidence associates psychiatric symptoms and stress with low birth weight, premature labor and delivery, and pregnancy complications (39–47). Therefore, if there is a link between prenatal psychiatric symptoms and inflammation, as we hypothesized and studies of non-pregnant women document, then that raises the possibility that symptoms may predict obstetric outcomes via their association with cytokine production. That follows reports in the obstetrics literature that inflammation in pregnancy predicts poor obstetric outcomes (48–51). We consider this an exploratory hypothesis because a very substantial number of individuals with pregnancy complications may be needed to detect this mediation (in contrast to the numbers needed to detect associations between symptoms and cytokines, the central aim of the paper).

In summary, the current study was designed to extend the limited research on psychiatric symptoms and proinflammatory cytokines in women with a normal pregnancy. We do this by a) focusing on a broad set of psychiatric dimensions (depression, anxiety and trauma) and targeting proinflammatory cytokines most reliably assessed in the clinical literature (IL-6 and TNF-α); b) including women at high psychosocial risk, who are typically under-represented in the literature; and c) assessing women in two occasions of measurement, during the 2nd and 3rd trimesters, to try to account for the changing nature of both symptoms and cytokines across pregnancy.

Methods

Design & Study Participants

The data are derived from a prospective, longitudinal cohort study of women receiving obstetrical care from a hospital-based practice serving a predominantly low income minority population. We included women who were physically healthy and considered low to medium obstetric risk as we wanted to examine the link between cytokines and affective symptoms in a normal, i.e. non-diseased state. High obstetric risk referred to increased likelihood of maternal or fetal complications due to various factors including young or old maternal age, more than one fetus, experiencing previous problems in pregnancy (preeclampsia, stillbirth, multiple miscarriages), drug or alcohol use. Women with existing medical conditions that would either raise obstetric risk or lead to increased cytokine levels were also excluded, including autoimmune disorders, high blood pressure, kidney disease and sexually transmitted diseases. Our inclusion criteria were therefore, women aged 20–34 years old with a confirmed singleton pregnancy less than 18 weeks gestation, considered low to medium obstetric risk by the medical team, with no existing autoimmune disorders, fluent in English and able to provide informed consent. Women diagnosed with bipolar disorder or schizophrenia were excluded. We obtained screening data on 214 women who were interested in participating in a pregnancy-related research study and willing to provide blood samples. Sixty-nine of these 214 women were excluded upon further interview. Fifty-two women had at least one exclusion criteria, including having autoimmune conditions not detected in the initial screen, being considered at increased obstetric risk, or presence of psychotic features. Seventeen women failed to complete both assessments; 9 relocated out of state or were lost to contact, and 8 experienced a perinatal loss or delivered prior to the 32 week assessment. We therefore report on a final sample of 145 women who completed assessments at both 18 and 32 weeks gestation. Data were collected between May 2007 and April 2010.

Ethical Approval

The study was approved by the University of Rochester Research Subjects Review Board. Written informed consent was obtained from each research participant following an explanation of the study procedures.

Procedure and Measures

The women were interviewed by trained clinical interviewers and completed a battery of questionnaires and a clinical diagnostic interview at approximately 18 and 32 weeks gestation. Interviews took place in the University of Rochester Clinical Research Center, located within the same hospital from which they received their obstetric care; blood was also obtained during these assessments. Detailed clinical, medical and sociodemographic data were obtained from case notes.

Depression—Depressive symptomatology was assessed using the Edinburgh Postnatal Depression Scale [EPDS] (52) the most widely used and validated screening tool for depressive symptoms in pregnant and postpartum women (53). Validation studies showed that a score of 13 on the EPDS identifies women with a diagnosis of major depression(54, 55), while a cut-off of ≥9 has been used within community samples to also include probable cases of minor depression. Clinical diagnoses of current depression and history of past depressive episodes were obtained through administration of the mood episodes section of the SCID (56), a widely used diagnostic assessment to assess clinical disorder.

Anxiety—Anxiety symptoms were assessed using the 20-item state subscale of the State-Trait Anxiety Inventory [STAI] (57), a widely used measure of anxiety in pregnancy in obstetric and psychological settings. The anxiety section of the SCID was completed to generate categorical diagnoses; Generalized Anxiety Disorder, Specific and Social Phobias, Obsessive Compulsive Disorder (OCD) and Panic Disorder were assessed. Exposure to traumatic events was categorized based on the responses given within the PTSD section; for those subjects reporting a traumatic event that met criterion A, each event and the age at which it occurred were described. Lifetime diagnoses of PTSD were made according to DSM-IV criteria.

Adverse Obstetric Outcomes—Obstetric outcomes were defined according to standard definitions, and their occurrence assessed from maternal and infant clinical case notes by a board certified specialist in Obstetrics & Gynecology and Maternal Fetal Medicine (EKP). The outcomes of interest were: premature labor and delivery (<37 weeks gestation), low birth weight (<2500g), growth restriction (<10^{th} percentile for gestational age), preterm premature rupture of membranes (<37 weeks and prior to onset of labor), preeclampsia, intra-uterine infection, placental abruption, gestational diabetes and rates of Caesarean sections, including those that were emergent (unscheduled) due to imminent maternal or fetal harm. We consider both number and type of events and a dichotomous index of any adverse obstetric outcome in analyses below.

Laboratory Procedures & Cytokine Analysis—The majority of blood samples were obtained between 8am and 2pm, although 14 samples were collected between 2pm and 4pm. Those women providing blood samples later in the afternoon did so at both time points. Blood was collected into vacutainer tubes (BD Diagnostics, Franklin Lakes, NJ) via conventional venipuncture. Blood was centrifuged at 1000g for 10 min within 15 minutes of collection and serum aliquoted into 4 cryovials to avoid repeat freeze-thaw cycles for testing. Serum was stored at −80°C until assayed. In order to ensure that elevated cytokines levels were not due to an underlying medical condition or infection, women were asked prior to the blood draw if they had been ill recently, the nature of any illness and any

medications that they had taken. Women who had been febrile, experienced a cold or flu or were taking medications for these were asked to return a week later, or when asymptomatic, to provide blood and complete assessments; we also investigated medical chart data for evidence of illness.

Serum levels of IL-6 and TNF-α were assayed with enzyme-linked immunoassay (ELISA) using high-sensitivity kits purchased from R&D Systems, Inc. (Minneapolis, MN). The kits were used according to manufacturer's standard protocols with the standard curve run on each 96-well assay plate. Samples were run in duplicate. Absorbance was read at 490 nm with 650 nm wavelength correction within 30 minutes after development using an automated Opsys MR Microplate Reader (Thermo Labsystems, Chantilly, Virginia). The minimum detectable limit for IL-6 is 0.039 pg/ml and 0.106 pg/ml for TNF-α. The intra-assay variability for both cytokines is approximately 4% and the inter-assay CV was <5%.

Data analysis

Subjects excluded due to elevated cytokine levels—Fifteen subjects had IL-6 and/or TNF-α levels that were highly elevated at 18 or 32 weeks gestation. In 6 cases, inspection of the medical notes showed that these individuals were being treated for infections that arose around the time of the blood draw and so these cases were excluded. However, we could not account for the remaining subjects with substantially clinically elevated cytokine levels, but presumed that the levels implied an undetected medical concern or idiopathic condition. We subsequently excluded subjects with IL-6 and TNF-α values >3 SD above the mean, resulting in N's of 130 and 137 subjects for analysis, respectively.

Covariates—Based on previous findings in the literature and following recent reviews (58) we included the following as covariates: maternal age, body mass index (BMI; calculated using the standard formula from the data taken at the initial intake when pregnancy-related weight gain is still very modest), education, Medicaid status, marital status, sleep (self-rated quality of sleep ranging from very bad to very good and the total number of hours slept in a typical night) (59) and the time of the blood draw. Number of hours of sleep and the time of the blood draw were included to control for circadian rhythm.

After reporting descriptive data, we report the associations between proinflammatory cytokines and individual health and socio-demographic factors previously linked with antenatal depression to determine which variables are important covariates for the main analyses. Analyses to examine the link between psychiatric symptoms and cytokines make use of the continuous (questionnaire) and categorical (SCID diagnosis) psychiatric data. We had no *a priori* predictions about the timing in pregnancy, and so we first report, for exploratory purposes, bivariate associations at each assessment. However, given the stability of individual differences across measurements, the most appropriate test is a repeated measures analysis of variance with time (18 and 32 weeks gestation) as a within-subjects factor and psychiatric symptoms (plus potential covariates) as between-subjects factors. That also allowed for the formal test of whether or not an association was significantly stronger in mid- than late-gestation. Repeated measures of analysis also models the dependence or within-individual correlation in measures over time. Meditational analyses were planned to test the hypothesis that psychiatric symptoms predicted obstetric outcomes via a shared link with cytokines (see below).

Cytokine levels were not normally distributed; the data were log transformed for subsequent analyses. Correlations between IL-6 and TNF-α across pregnancy were <.10; consequently, they were treated separately in analyses of psychiatric and obstetric data.

Results

Preliminary analyses

Descriptive data, shown in Table 1, indicate that the sample was at generally high psychosocial risk of mood disorders, indexed by the high rates of minority status, low education, non-married status, Medicaid receipt, and age at first pregnancy.

Psychiatric data (see Table 2) confirm this impression: 15.2% and 11.2% of women met DSM criteria for minor or major depression at 18 and 32 weeks gestation respectively; 38.6% of women scored ≥9 and 20% >12 on the EPDS at 18 weeks, while at 32 weeks 28.2% scored ≥9 and 12% were >12. Thirty-two percent of women met criteria for an anxiety disorder (excluding PTSD) during pregnancy and over a third (37.2%) had been exposed to a traumatic event, with 11% having a lifetime diagnosis of PTSD.

Analyses were conducted both with and without the blood samples that were collected between 2–4 pm; similar results were obtained in both analyses and so we report data based on the whole sample (e.g., the correlation between time of assessment and cytokine levels were r=−0.02 and r=0.12 for IL-6 and r=−0.07 and r=0.09 for TNF-α at 18 and 32 weeks). Table 3 shows mean levels of IL-6 and TNF-α at both points. Both cytokines increased significantly across pregnancy and showed significant intra-individual stability across time.

For descriptive purposes we present significant correlations between cytokine levels and health and sociodemographic factors. We found that BMI was significantly positively correlated with IL-6 at both times in pregnancy (r=0.45 p<.001 at 18 weeks, and 0.37 p<. 001at 32 weeks gestation).

For IL-6 at 18 weeks gestation we found significant negative correlations with age at first pregnancy (r(130)= −0.20, p<0.05) and number of hours of sleep (r(121)=−0.22, p<0.02). We also found that, at 18 but not 32 weeks gestation, parous women had higher mean levels of IL-6 (values in pg/ml) than those without children (1.04 (0.36) vs 0.91 (0.39); (F 1,128)=4.20, p<0.05) and white women had lower levels of IL-6 compared with minority women (0.87 (0.48) vs 1.01 (0.34); F 1,128=5.90, p<0.02). IL-6 at 32 weeks gestation was significantly negatively correlated with number of years of education (r(130) = −0.21, p<. 02.

The only significant finding for TNF-α was between age at first pregnancy and TNF-α levels at 18 weeks gestation (r(137)= −.23, p<.01). We consider these covariates in the analyses below.

Psychiatric Symptomatology & Cytokines—There was no evidence of a significant link between depressive symptoms and IL-6 in pregnancy. Bivariate correlations between EPDS continuous scores and IL-6 were <r =.10; categorical analyses using SCID-based diagnoses of Major Depressive Disorder (MDD) or a broader phenotype that included minor depression and the NOS designation yielded a similar lack of association. Repeated measures analysis of variance, which capitalized on the power of the repeated assessments, showed no significant association between depression (F(1,128)=1.00, p>.10) or depressive symptoms and IL-6 (F(1, 128)=1.15, p>.10). Moreover, whereas we observed a sizeable increase in IL-6 across pregnancy (Table 3), the mean level of depressive symptoms on the EPDS decreased (Table 2), providing yet further evidence of a disconnect between depression and IL-6. Parallel analyses for TNF-α also revealed a lack of association and very small effect size (F 1,135)p>.96; F (1,135)p>.23). See Table 4 for mean, standard deviations and effect sizes for depression and cytokine analyses.

There was no evidence of a significant association between anxiety and IL-6 or TNF-α, according to the continuous measure (STAI) or categorical diagnoses of any anxiety disorder, excluding PTSD, from the SCID (see Table 4). These findings were unchanged when we repeated the above analyses controlling for BMI, ethnicity, number of children, time of blood draw, age at first pregnancy, and education.

We did, however, observe a significant association between trauma and TNF-α. Repeated measures of analysis of variance indicated a main effect of trauma exposure and TNF-α ($F(1,135)=4.43$ $p<.05$); the effect of time was also significant ($F(1, 135)=18.63$ $p<0.001$), but there was no significant interaction between time and trauma exposure in predicting TNF-α levels ($F(1, 135)=0.36$; $p>.20$; Figure 1). The main effect of trauma exposure remained significant after controlling for covariates (time of blood draw, age at first pregnancy, maternal age, ethnicity, education), including co-occurring depression and anxiety.

Further analyses of the trauma exposed group (n=54) found no link between the age at first trauma and TNF-α level. We found that TNF-α and lifetime clinical diagnosis for PTSD (n=16) were less strongly linked when compared to those women with trauma exposure but no PTSD diagnosis In a repeated measures analysis of variance, the effect of PTSD diagnosis was not significant ($F(1,135)= 1.75$, $p>.20$), with time remaining significant ($F(1,135)=11.80$, $p<0.001$) and no significant time × diagnosis interaction.

We did not find a significant association between trauma exposure or PTSD diagnosis and IL-6, when parallel repeated measures analyses were conducted (details available from the first author).

Obstetric Outcomes—Psychiatric symptoms and diagnoses at either point in pregnancy did not predict obstetric outcomes (birthweight, gestational age, complications); correlation coefficients did not exceed r=.15. Neither did we obtain a significant association between IL-6 or TNF-α and birthweight, gestational age, or complications ($r's < .15$ in absolute value). Given the lack of prediction of obstetric outcomes, we did not pursue the multivariate analyses linking psychiatric symptoms, cytokines, and obstetric outcomes.

Discussion

The hypothesis that proinflammatory cytokines may be involved in the pathophysiology of psychiatric symptoms is gaining considerable momentum and is supported by both animal and human data. Nonetheless, the mechanisms underlying this connection and its application to treatment remains largely unresolved. We extended this line of investigation to the prenatal period in a short-term longitudinal study that followed a sample of women at high psychosocial risk, but with normal pregnancies.

We found no relationship between IL-6 and TNF-α at either time point in pregnancy, supporting the findings of previous studies of pregnant (16–18) and non-pregnant samples (19). Although IL-6 and TNF-α are both proinflammatory cytokines and play a major role in the acute phase response, they do differ functionally and so the lack of association is not wholly surprising.

We found limited but robust evidence of a link between trauma exposure and elevated TNF-α; no other reliable link between symptoms and proinflammatory cytokines was detected. The current study provides a first documentation in pregnancy of an association between trauma and TNF-α, a cytokine that is among the most widely-investigated in the psychiatric literature. This extends prior work linking trauma and proinflammatory cytokines in non-

pregnant samples (30–33, 60) in suggesting that one of the effects of trauma exposure may be inflammation. In this study, the elevated proinflammatory marker associated with past trauma persisted throughout pregnancy and was found despite the substantial normative changes in immunological markers (and many others besides) that occur in pregnancy. It is notable that the effect observed here is comparable to that observed in the non-pregnant samples (see above). We are unable to specify the mechanism linking trauma exposure and TNF-α levels, but several candidates exist and require further study (see 61).

Exposure to stressors, including traumatic events, leads to alteration of the sympathetic and parasympathetic nervous systems and the hypothalamic-pituitary-adrenal (HPA) axis (62). The bidirectional relationship between the HPA axis and immune system can be disrupted as a consequence (62–64), leading to greater proinflammatory immune responsiveness (65). It may be that for women that have been exposed to a traumatic event the elevated proinflammatory state persists despite the immunosuppression ordinarily seen during pregnancy (35). However, we need to further examine the relationship between cytokines and trauma exposed women in both the postpartum period and a non-pregnant state.

Compared to previous studies of pregnant women and depressive symptoms (14,36,37) we report higher levels of IL-6 and lower levels of TNF-α in our sample. Our observation of small effect sizes, in some cases opposite to that predicted, between IL-6 and mood symptom ratings also contrasts with previous studies of non-pregnant individuals (29, 33, 60). There are several possible explanations for this discrepancy. One is pregnancy itself. As noted, pregnancy-induced changes in IL-6, which resulted in a change of approximately one-third of a standard deviation from approximately 18 to 32 weeks gestation, may have confounded an association that would be otherwise detected (i.e., outside of pregnancy). That is not wholly convincing, however, because two studies did report an association between IL-6 and self-reported symptoms and stress in pregnancy, although the psychiatric phenotype assessed differed between studies (stress versus depressive symptoms) (36, 38). Another possibility for these apparent differences in both cytokine levels and their link with depression between studies is that our sample differed; these women were at particular psychosocial risk due to factors associated with low SES (less years of education, single, Medicaid recipients) and almost half were from a minority group. Whether these factors may disrupt a link between IL-6 and mood symptoms remains to be determined, and will require further follow-up into the postnatal period.

We did not find support for our exploratory hypotheses. TNF-α, which was associated with trauma, did not predict obstetric outcome; neither did IL-6 nor the other symptom measures. That was an important set of analyses to conduct because previous studies suggested that trauma-exposed woman may have worse obstetric outcomes (66). Birth outcomes were included in our framework because they were not included in previous studies of symptoms and cytokines (36–38) and it is clearly important to examine if the overlap between symptoms and cytokines accounted for a link between psychiatric symptoms and obstetric risk. This null finding must be seen as preliminary, however, because significant prediction from prenatal symptoms to obstetric outcome are typically derived from large community samples, and documenting a mediation effect may similarly require very large samples. Also, we excluded medically medium-high risk pregnancies and so we have excluded the population for whom the psychiatric symptom and proinflammatory cytokine link may be most easily detected. A further consideration is that, as we and others have found, apparently normal samples almost inevitably include individuals with substantially elevated cytokines. It is certainly possible that previously observed relationships may not be demonstrable under pathophysiological conditions. Quite apart from the biological explanation is the practical issue of how these apparently “extreme” cases are best handled.

Our study is limited in that we focused on low medical risk pregnancies and so had a low base rate of adverse outcomes; large scale studies may be required to show effects of psychiatric symptoms or increased inflammation on adverse outcomes. Balancing these limitations are several strengths, including the moderately sized sample, multiple occasions of measurement from pregnancy to birth outcome, detailed symptom and psychiatric assessments, inclusion of several potential confounds of cytokine levels, and focus on specific biomarkers of inflammation.

The study provides data on the link between cytokines and mood symptoms during pregnancy. The finding of TNF-α predicting trauma exposure in pregnant women requires further investigation as it may be a potential predictor of affective disturbance in the postpartum period.

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Acronyms used

IL	interleukin
TNF	tumor necrosis factor
PTSD	post traumatic stress disorder
IFN	interferon
EPDS	Edinburgh Postnatal Depression Scale
STAI	State-Trait Anxiety Inventory
DSM	Diagnostic and Statistical Manual
SCID	Structured Clinical Interview for DSM
BMI	body mass index
MDD	Major Depressive Disorder
NOS	not otherwise specified
HPA axis	hypothalamic-pituitary-adrenal axis

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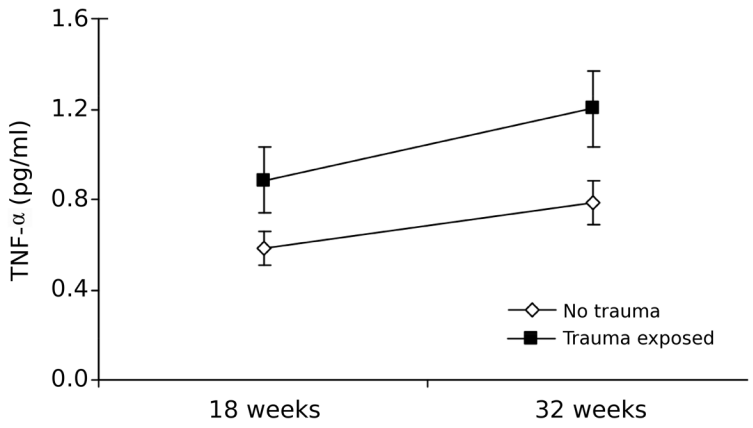

Figure 1.
Mean levels of TNF-alpha across gestation by trauma exposure status. Standard error bars are shown.

Table 1

Key sociodemographic and clinical variables of the sample.

Variable	M (SD) range or % (n)
Age at interview (years)	24.67 (3.66) 20–34
Age at first pregnancy (years)	19.52 (4.01) 11–34
First pregnancy ≤ 18 years old	48.3% (70)
Total number of pregnancies	1.71(1.62) 0–8
Is this the first pregnancy?	
Yes	29.0% (42)
Number of children	1.02(1.12) 0–4
0	42.1% (61)
1	30.3% (44)
2	13.8% (20)
3+	13.8% (20)
Education	
Years completed	12.73(2.27) 8–26
Did not finish high school	20.7% (30)
Completed high school	41.4% (60)
Some college	25.5% (37)
Completed college	12.4% (18)
Ethnicity	
White/Caucasian	29.0% (42)
Black African American	46.2% (67)
Biracial	6.2% (9)
Hispanic/Latina	16.6% (24)
Other	2.1% (3)
BMI	28.06 (7.61) 13.0–49.4
Underweight (<18.5)	5.5 % (8)
Normal (18.5–24.9)	37.9 % (55)
Overweight (25.0–29.9)	23.4 % (34)
Obese (>30)	33.1 % (48)
Marital Status	
Single	51.0% (74)
Cohabiting	28.3% (41)
Married	20.7% (30)
Receiving Medicaid	70.3% (102)
Low birthweight <2500g *	6.3% (9)

Variable	M (SD) range or % (n)
Premature delivery <37 weeks *	3.5% (5)
Intrauterine growth restriction*	4.9% (7)
Premature Rupture of Membranes*	1.4% (2)
Preeclampsia*	4.2% (6)
Placental Abruption*	1.4% (2)
Gestational Diabetes*	5.6% (8)
Rates of Caesarean-sections*	19.0% (27)
Emergent Caesarean-sections	25.9% (7/27)

*Sample n=142 for these variables, for all others n=145.

Table 2

Psychiatric diagnoses and symptoms across pregnancy.

Psychiatric Diagnosis/Symptoms	Mean (SD) range or % (n)
Major Depressive Episode	
18 weeks	6.9% (10)
32 weeks	6.3% (9)
Minor depression or NOS	
18 weeks	8.3% (12)
32 weeks	4.9% (7)
Self-reported history of depressive episode	46.9% (68)
EPDS Score	
18 weeks	7.23 (5.99) 0–23
32 weeks	5.90 (5.32) 0 – 24
>12 at 18 weeks	20.0% (29)
>12 at 32 weeks	12.0% (17)
Diagnosis of Any Anxiety Disorder in Pregnancy excluding PTSD	31.7% (46)
Lifetime Diagnosis of PTSD	11% (16)
Met criterion A for PTSD	37.2% (54)
Age at first traumatic exposure (years)	15.74 (6.49) 4–29
Exposure to trauma <18 years old	64.8% (35)

Table 3

Mean levels of IL-6 and TNF-α in serum across pregnancy (pg/ml).

	18 weeks gestation Mean (sd)	32 weeks gestation Mean (sd)	Statistics from Time 1 to Time 2.
IL-6	0.99 (0.38)	1.16 (0.37)	t=6.21, df=129, p<0.001. r=0.66, 130, p<0.001.
TNF-α	0.44 (0.41)	0.55 (0.45)	t=4.30, df=136, p<0.001 r=0.73, 137, p<0.001

Table 4

Bivariate analysis of mean levels of cytokines (pg/ml) by PTSD diagnostic category and gestation point with effect size (Cohen's d).

	IL-6 (n=130)		TNF-α (n=137)	
Diagnostic Category	**18 weeks Mean (sd) Cohen's d**	**32 weeks Mean (sd) Cohen's d**	**18 weeks Mean (sd) Cohen's d**	**32 weeks Mean (sd) Cohen's d**
PTSD Lifetime Diagnosis				
Yes	1.07 (0.43)	1.26 (0.44)	0.53 (0.39)	0.71 (0.44)
No	0.98 (0.37)	1.14 (0.36)	0.43 (0.41)	0.53 (0.45)
	d=0.22	d=0.30	d=0.25	d=0.40
Trauma Exposure according to PTSD criterion A				
Yes	1.02 (0.39)	1.18 (0.39)	0.52 (0.45)	0.66 (0.51)
No	0.97 (0.36)	1.14 (0.36)	0.39 (0.37)	0.49 (0.41)
	d=0.13	d=0.11	d=0.32	d=0.37

*N's for those meeting PTSD lifetime criteria diagnostic criteria: IL-6=15, TNF-α=16 and criterion A of PTSD (IL-6=50, TNF-α=53).