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Prepartum Depressive Symptoms Correlate Positively with C-Reactive Protein Levels and Negatively with Tryptophan Levels: A Preliminary Report

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Abstract

Prepartum and postpartum depression have negative, and sometimes devastating, effects on women and their families. As inflammatory processes are related to depression in general, we hypothesized that inflammatory perturbations, prepartum and postpartum, contribute to triggering and worsening of symptoms of peripartum depression. We conducted a longitudinal preliminary study on 27 women at high risk for developing postpartum depression measuring SIGH-SAD scores at three time points: 35-38 weeks gestation, 1-5 days postpartum, and 5-6 weeks postpartum. Serum C-reactive protein and interleukin-6, both markers of inflammation, as well as tryptophan, kynurenine, and the kynurenine/tryptophan ratio, as consequences of inflammation and pathophysiological steps towards depression, were measured at each time point. C-reactive protein levels were found to be positively related to atypical and total depression scores in the prepartum period and with atypical depression scores in the early postpartum period. Tryptophan was found to be negatively associated with total depression scores in the prepartum, as well. These findings warrant further investigation that could lead to novel interventions to decrease poor outcomes from peripartum depression.

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Keywords

Prepartum depression; postpartum depression; atypical depression; inflammation; C-reactive protein; tryptophan; tryptophan depletion; kynurenine

Introduction

Peripartum, or perinatal, depression includes the well known postpartum depression, the very common postpartum blues, and the less known and recognized prepartum depression. Yet, prepartum depression, which occurs in 8.5 to 11% of women (1), has a potentially detrimental impact not only on the mother, but also on the offspring, including an increased risk of spontaneous preterm birth (2,3), poor fetal growth (4-6), and infant temperament reactivity (7). Often times, prepartum depression is undiagnosed due to common pregnancy symptoms, such as fatigue, weight gain, and sleep problems, that are similar to major depression criteria. Prepartum depression is also a high risk factor for the development of postpartum depression (8), a disorder with negative consequences of impaired mother-child interactions (9), chronic depression (10), suicide (11), and, rarely, infanticide (12). In fact, about 10-12% of postpartum depression has a prepartum onset (13,14).

Activation of the immune system and production of cytokines has been proposed as a potential mechanism that may promote depressive states (15). Administration of certain cytokines to patients for therapeutic purposes and induction of cytokines experimentally in healthy subjects can result in depression (16-19). Maternal immune system changes during pregnancy include evidence of immune system activation, immune system suppression, and immunological tolerance (20-23). These changes are, in great part, physiological. For instance, for a viable pregnancy, the maternal immune system must tolerate paternal-derived fetal antigens. In contrast, the mother physiologically requires a more vivid immune response in preparation for delivery, considering the associated massive tissue trauma and exposure to bacterial microorganisms. Consistent with their biological functions, measured cytokines levels are higher in women at the end of term, compared to non-pregnant women (24). After delivery, there is even greater immune activation, with increased serum concentrations of several inflammatory markers such as interleukin-6 (IL-6), IL-6 receptor (IL-6R), IL-1 receptor antagonist, and decreased levels of leukemia inhibitory factor receptor (24). A previous study showed that women who were more depressed in the early postpartum had significantly higher serum concentrations of IL-6 and IL-6R (24), suggesting a potential involvement of this cytokine in postpartum depression.

There are several potential biological mechanisms connecting inflammatory processes with mood dysregulation. One of them is the serotonin dysfunction secondary to the activation of the enzyme indoleamine 2,3 dioxygenase (IDO) by cytokines, resulting in tryptophan depletion and production of compounds such as kynurenine (KYN) (25). Tryptophan (TRP) is the precursor of serotonin (5HT), which plays an important role in major depression and other mood disorders. Studies have found that TRP depletion is correlated with inducing depressive symptoms, particularly in patients with a history of major depressive episode and/or recently medicated or partially remitted symptoms (26-28). In an alternative enzymatic pathway via IDO, TRP can be metabolized to KYN and, thus, less TRP is available to be metabolized to 5HT (29). There is evidence that plasma tryptophan concentrations in women at the end of term and after delivery are lower than plasma tryptophan concentrations in non-pregnant, healthy women (30,31) and that plasma tryptophan concentrations decrease with the duration of pregnancy (32). Moreover, the decrease in the plasma KYN/TRP ratio is significantly more pronounced in women with high levels of depressive symptoms in the early postpartum period (33). Not only could tryptophan depletion result in depression in vulnerable postpartum

women, but metabolites of kynurenine are potentially toxic compounds. The putative mechanism connecting decrease in KYN/TRP ratio and inflammation is the activation of IDO by pro-inflammatory cytokines released during inflammation.

We thus hypothesized that there is a relationship between inflammatory markers, TRP, KYN, and the KYN/TRP ratio, and symptoms of depression in prepartum and postpartum women.

Methods

In this preliminary study, twenty-seven women were recruited from two Mid-Atlantic obstetric clinics and one birthing center and evaluated for depression, inflammatory markers, and KYN/TRP ratio at three time points: 35-38 weeks gestation (prepartum), 1-5 days postpartum (early postpartum), and 5-6 weeks postpartum (late postpartum). Participants signed informed consent after a full explanation of the study, and were evaluated to sign consent, as approved by the Institutional Review Board of the University of Maryland Baltimore.

Screening

The obstetricians and midwives completed an inclusion-exclusion criteria checklist for all pregnant women at their clinics. Women were excluded if they had any autoimmune disorders, if they abused alcohol, opiates, cocaine, psychostimulants, marijuana, or sedatives during current pregnancy, if they had a lifetime diagnosis of psychotic illness including a history of psychotic depression or infanticide, a lifetime diagnosis of alcohol, phencyclidine, hallucinogen, cannabis, opiate, cocaine, or stimulant dependence, if they had any active infections, or were using antidepressant medications during the current pregnancy.

Women interested in participating were screened with the mood disorder, substance abuse screen, and psychotic screen modules of the Structured Clinical Interview Diagnostic for DSM-IV TR (SCID) (34) for inclusion criteria and to confirm no exclusion criteria. As we wanted to study women who were more likely to develop postpartum depression, we included women who scored positive for factors predicting postpartum depression. As such, women were included if they were at least 18 years of age and had a lifetime history of major recurrent mood disorders, an anxiety disorder symptomatic during pregnancy, or at least one of the stressful social situations known to be high risk factors for postpartum depression during the past year: death of a loved one, separation from partner/boyfriend/husband, loss of job, and/or moving from household.

Procedure

The Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder (SIGH-SAD) (35) was used to measure severity of depression in study participants. Trained raters asked participants 29 questions at 3 different times: 35-38 weeks gestation (prepartum), days 1-5 postpartum (early postpartum), and weeks 5-6 post-partum (late postpartum). This scale includes typical depressive symptoms and atypical depressive symptoms. Ten milliliters of venous blood was drawn from each participant in the prepartum, early postpartum and late postpartum for C-reactive protein (CRP), IL-6, TRP, and KYN. After centrifugation at 3,000 rpm for 10 minutes, serum was separated and frozen at -70 degrees Celsius. IL-6 and CRP were measured by two antibody ELISAs in the University of Maryland Cytokines Core Laboratory (www.cytokines.com) using paired antibodies and standards from 0.08 mcg/mL and 1.5 pg/mL for CRP (Dako, Glostup, Denmark) and IL-6 (Pierce/Endogen, Rockville, IL, USA) respectively. Levels of IL-6 and CRP were calculated from a standard curve using the SoftPro software package (Molecular Devices, Sunnyvale, CA, USA). TRP and KYN measurements were done using HPLC on reversed phase [36]. Serum samples were diluted with potassium phosphate buffer containing L-nitro-tyrosine as internal standard and

were deproteinized with trichloroacetic acid. After injection of 100 μL, separation was performed on a reverse phase C18 column (Lichrocart, Merck, Darmstadt, Germany) using sodium acetate buffer (15 mmol/L, pH 4.0) with 3% acetonitril and a flow rate of 0.9 mL/min at a temperature of 25°C and a Varian ProStar liquid chromatography system with autosampler Model 400 (Varian, Palo Alto, CA, USA). L-kynurenine was monitored by its UV-absorption at 360 nm (UV-detector SPD-6A, Shimadzu, Japan), tryptophan by detection of its natural fluorescence at 285 nm excitation and 365 nm emission wavelengths (ProStar fluorescence-detector Model 360, Varian). Peaks were identified by comparing their retention time to those of an albumin-based calibrator containing 10 μmol/L L-kynurenine and 100 μmol/L L-tryptophan which was prepared like the serum samples. To estimate IDO activity, KYN/TRP was calculated.

Data analysis

Initial descriptive analyses included examining distributions of all variables for outliers and extreme skewness. Two outliers were identified and all analyses conducted both with and without them; results were very similar. Analyses presented are without outliers. Means and standard deviations were calculated for all depression scores and biomarkers. Statistical comparisons across the three time periods were made using repeated measures (mixed model) regression analyses to account for within-subject correlation. Associations of biomarkers with depression scores were estimated with mixed model regression analyses as well.

Results

Twenty nine women were recruited for the study. Two women dropped out after one measurement, leaving 27 women who completed the study. A majority of the sample was African American (85%), never married (74%), and multiparous (63%). The mean age was 23.2 years (*SD* = 6.6 years). According to the SCID results, 52% percent of the sample had no past or current mood disorder. Eight women had past history of major depression and two had current depression during their pregnancy (see Table 1).

Depression Scores

Total depression scores were higher in the prepartum (M = 11.4, *SD* = 6.9) than the early postpartum (M= 9.3, *SD* = 6.6) and the late postpartum (M = 7.9, *SD* = 4.6). Atypical depression scores were significantly higher in the prepartum (M = 4.9, *SD*= 3.3) than the early postpartum (M = 3.5, *SD* = 2.7) and the late postpartum (M = 3.5, *SD* = 3.1) (*p* = .04, Table 2).

Inflammatory Markers

CRP and atypical depression scores prepartum were positively correlated (*r* = .59, *p*=.005). For every one mcg/mL increase in CRP, there was a 0.13 point increase in atypical scores (*p*=.02) and a 0.18 point increase in total depression score (*p*=0.03, Table 3).

CRP was negatively associated with total and atypical depression scores in the early postpartum, but there was no association in the late postpartum. There were no significant relationships between IL-6 and total or atypical depression scores at any time points.

Tryptophan

TRP was significantly higher in the late postpartum (M = 50.0, *SD* = 7.0) than the prepartum (M = 44.9, *SD* = 9.5) (p = .002) and the early postpartum (M = 44.2, *SD* = 7.8) (*p* <.001). KYN was also significantly higher in the late postpartum (M = 1.7, *SD* = 0.5) than the prepartum (M =1.4, SD = 0.4) and the early postpartum period (M = 1.4, *SD* = 0.4) (*p* =.004). The KYN/TRP ratio was lower in the prepartum period (M = 32.8, *SD* = 7.3) than the early postpartum period

(M = 34.2, *SD* = 11.3) and the late postpartum (M = 34.8, *SD* = 8.6). However, changes over time in KYN/TRP ratio scores were not significant. TRP was significantly negatively associated with total depression score in the prepartum period, but not in other time periods. Neither KYN nor the KYN/TRP ratio was associated with depression scores.

Discussion

This is the first study, to our knowledge, to examine the relationship between inflammatory markers and peripartum depression, separately for typical and atypical symptoms. In fact, we identified associations with biological markers only with atypical and total depression scores, and we did not find any association with typical depression scores. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (37) lists "with atypical features" as a specifier of major depression. To be diagnosed with this identifier, the person must have mood reactivity, such as mood brightening in response to actual or potential positive events, and two or more of these symptoms: significant weight gain or appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity. Women are more likely to have atypical symptoms than men (38-41). However, it is not unusual for women in their third trimester to experience fatigue or sleepiness secondary to sleep disturbance due to fetal movement and difficulty breathing, and weight gain due to pregnancy. In the present study, any weight gain due to pregnancy (weight gain 1-2 lbs/week) was not counted in the depression scores so as to determine depressive symptoms versus normal physiological changes. Many studies do not assess atypical symptoms for major depression in the prenatal or postpartum period; therefore it is hard to determine the incidence in the prenatal period (42).

The only finding consistent with the hypothesized relationship between inflammation and mood dysregulation was the positive relationship between depressive symptoms, both atypical and total, and CRP. Elevated CRP was found in another sample of non-pregnant women with remitted major depressive disorder [43] and a mostly female sample of currently depressed patients (44). In response to tissue injury or stress, pro-inflammatory cytokines (TNF-α, IL-1beta, IL-6) are released from macrophages. These cytokines induce the release of certain acute phase proteins, such as CRP, into the plasma. CRP, produced mainly by the liver, is a more stable measure of inflammatory process than other, more transient, markers, such as IL-6.

Of interest also was the observed negative association of TRP with total depression scores in the prepartum period. Our results are consistent with the previously reported TRP degradation occurring during gestation and improved during the postpartum period (45). Inflammation has been found to contribute to TRP depletion via activation of the IDO metabolic pathway (25). Subsequently, reduced tryptophan levels lead to decreased synthesis of serotonin in the brain. The KYN/TRP ratio in our study was elevated in the early postpartum compared to the prepartum period, although slightly and nonsignificantly. This is not inconsistent with a recent study in which TRP increased and KYN/TRP decreased in women who did not report symptoms of postpartum blues, and showed no change in women with postpartum blues (46).

Our study had several limitations. Despite being at risk, many of the women did not develop postpartum depressive symptoms and, thus, our hypothesis needs to be reevaluated in larger cohorts or in case control paradigms in other studies where serum or plasma have been preserved. As mentioned, we measured IL-6 and not other pro-inflammatory cytokines such as TNF α and IL-1. In this preliminary study, our sample was small ($n = 27$), thus generalization of our findings is limited. Lastly, we acknowledge that depressive symptoms, especially atypical symptoms, may overlap with sickness behavior symptoms. Other important biological markers, such as cytokines or hormones have not been measured.

Conclusions

This study adds to the very limited literature on prenatal depression and to the growing body of literature linking mediators of inflammation with depression. Confirming and expanding our results in larger samples, and identifying pathophysiological mechanisms which may contribute to perinatal depression, may result in identifying new treatment targets and finding novel interventions, leading to better health, symptomatic relief, and improved quality of life in women and their children.

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Table 1

Demographics of the sample (n=27)

Demographics	Category	% (*n*)
Race	African American	85% (23)
	White	15% (4)
Marital Status	Married	22% (6)
	Never married	74% (20)
	Other	0.03% (1)
Level of Education	Less than high school	19% (5)
	High School graduate	48% (13)
	Part college	19% (5)
	Graduate 2 year college or more	15% (4)
Parity	Primiparous	37% (10)
	Multiparous	63% (17)
Psychiatric Diagnosis	Major Depression recurrent, (current episode)	0.1% (2)
	Major Depression Recurrent (past episode)	30% (8)
	Depressive Disorder Not Otherwise Specified	11% (3)

Table 2

Means of total and atypical depression scores, C-reactive protein, Interleukin-6, Tryptophan, Kynurenine, and Kynurenine/Tryptophan ratio (n =27)

		Mean	SD
Total Depression Scores	Prenatal	11.4*	6.9
	Early Postpartum	9.3	6.6
	Late Postpartum	7.9	4.6
Atypical Depression Scores	Prenatal	4.9*	3.3
	Early Postpartum	3.5	2.7
	Late Postpartum	3.5	3.1
C-Reactive Protein (μg/L)	Prenatal	20	15.3
	Early Postpartum	41.2**	20.4
	Late Postpartum	15.5	18.6
Interleukin 6 (pg/mL)	Prenatal	10.2	7.4
	Early Postpartum	60.4**	77.3
	Late Postpartum	11.9	10.1
Kynurenine/ Tryptophan ratio μmol/mmol	Prenatal	32.8	7.3
	Early Postpartum	34.2	11.3
	Late Postpartum	34.8	8.6
Tryptophan (μmol/L)	Prenatal	44.9	9.5
	Early Postpartum	44.2	7.8
	Late Postpartum	50.0#	7.0
Kynurenine (μmol/L)	Prepartum	1.4	0.4
	Early Postpartum	1.4	0.3
	Late Postpartum	1.7#	0.5

* significantly higher than postpartum values, $p<0.06$.

** significantly higher than pre- and late postpartum values, $p<0.001$.

significantly higher than pre- and early postpartum values, $p<0.005$.

Comparisons of means from mixed model analyses, adjusting for repeated measures on participants.

Table 3

Associations of biomarkers with depression scores prepartum, early postpartum, and late postpartum, from repeated measures regression analyses (n=27)

Independent Variable	Total Depression Scores		Atypical Depression Scores	
	Coefficient	P value	Coefficient	P value
C-Reactive Protein				
Prepartum	0.176	0.03	0.126	0.002
Early Postpartum	-0.098	0.09	-0.060	0.03
Late Postpartum	-0.002	0.98	0.011	0.75
Tryptophan				
Prepartum	-0.277	0.04	-0.077	0.27
Early Postpartum	0.049	0.77	0.037	0.67
Late Postpartum	-0.112	0.53	0.005	0.95
Kynurenine				
Prepartum	-4.29	0.22	-0.53	0.77
Early Postpartum	-0.47	0.90	1.85	0.34
Late Postpartum	-3.87	0.17	-0.05	0.97
Interleukin 6				
Prepartum	-0.093	0.60	0.089	0.32
Early Postpartum	0.007	0.68	0.003	0.75
Late Postpartum	-0.133	0.35	-0.088	0.23