Do pregnant women with depression have a pro-inflammatory profile?

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Abstract

Aim: We tested the hypothesis that maternal depression is associated with a pro-inflammatory state in pregnancy.

Material and Methods: In this nested case–control study, pro-inflammatory cytokine levels were compared between women with depression in pregnancy (n = 100) and a computer-generated referent group of healthy women known not to be depressed (n = 100). We only included cases with a documented Diagnostic and Statistical Manual of Mental Disorders depression diagnosis in the current pregnancy. Serum samples drawn at 11–14 weeks of gestation were analyzed for levels of tumor necrosis factor-alpha and interleukin-6 using high-sensitivity immunoassays.

Results: Maternal demographics were similar between the groups except for older age (34.1 vs 32.7 years, P = .05), and lower body mass index (27.3 vs 28.9 kg/m², P = 0.03) among the depressed subjects. Compared to control women, tumor necrosis factor-alpha (5.8 ± 3.4 vs 3.2 ± 2.8 pg/ml, P < 0.0001) and interleukin-6 (2.4 ± 3.8 vs 1.5 ± 1.4 pg/ml, P = 0.03) levels were higher among women with depression. The higher rate of inflammatory cytokines remained significant after controlling for potential confounders, including maternal age and body mass index.

Conclusion: Women with depression may have higher levels of inflammatory markers in early pregnancy. Our findings support the hypothesis that inflammation may be a mediator in the association between maternal depression and adverse perinatal outcomes.

Key words: cytokines, depression, inflammation, pregnancy, stress.

Introduction

Pregnancy is a time of biologic ‘stress’ as the maternal systems prepare to support normal fetal development. Additional external maternal stressors, such as financial concerns, racism, and coincident psychiatric disease, also have the potential to negatively impact the pregnancy. In fact, there is a growing body of epidemiologic literature linking maternal psychosocial stress to adverse pregnancy outcomes.¹–⁶ Stress occurs when environmental (internal or external) demands tax or exceed the adaptive capacity of an individual. Stress is complicated to measure, is multi-factorial, and includes both acute and chronic exposures that are likely cumulative. One important health risk related to chronic stress is its deleterious effect on immune function.
Stress affects cellular immunity, with a concomitant increase in severity or duration of infections, poor wound healing, and reactivation of latent viruses. \textsuperscript{7–10} Considerable evidence has accumulated linking chronic stress with adverse perinatal outcomes. Similarly, research has demonstrated that excessive inflammation is associated with increased risk for adverse maternal–fetal outcomes, including gestational hypertension and prematurity. \textsuperscript{11} Therefore, it has been postulated that stress may exact its impact on pregnancy through an inflammatory pathway. \textsuperscript{12} Indeed, several recent studies have demonstrated conflicting results regarding an association between perceived maternal stress and depressive symptoms with a generalized pro-inflammatory state. \textsuperscript{13–14} Furthermore, research has demonstrated racial-ethnic disparities in pro-inflammatory cytokine profiles, which supports the hypothesis that race/ethnicity-related risks for adverse perinatal outcomes are related to stress. \textsuperscript{15–17} Consequently, using maternal depression as a proxy for stress, our aim was to test the hypothesis that maternal depression is associated with a disproportionate pro-inflammatory state in pregnancy.

Methods

In this nested case–control study, we accessed the records of all 4,225 women who had previously given blood for routine genetic multiple markers screening and subsequently delivered at a single tertiary hospital, between July 2004 and July 2009. All women, regardless of risk status or payer status, were offered this screening as part of routine prenatal care. Non-fasting blood samples were collected for routine genetic multiple marker screening between 11 and 14 weeks of gestation, and serum aliquots were barcoded and frozen at \textdegree C. Maternal demographic and medical data were abstracted from the medical record. The Institutional Review Board approved this study prior to data collection, and permission was obtained to use banked serum from these women for research purposes.

Using a standard data collection sheet, demographic characteristics, obstetric, and neonatal outcome data were abstracted from the prenatal and inpatient records. The following maternal characteristics were based on self-report: height, pre-pregnancy weight, smoking, illicit substance use, and date of last menstrual period. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. Maternal body mass index was calculated from the patient’s reported height and pre-pregnancy weight. Other abstracted variables included race/ethnicity, maternal health insurance type (private or public), chronic maternal illness, and antidepressant medication use.

We included term deliveries (\( \geq 37 \) weeks) among women diagnosed with depression (cases) prior to pregnancy. In order to verify the clinical diagnosis of depression, we restricted our cases to women who received care in our Perinatal Mood Disorders Clinic, and had a documented \textit{Diagnostic and Statistical Manual of Mental Disorders} depression diagnosis by a provider in the present pregnancy. The Perinatal Mood Disorders Clinic is operated under the umbrella of the institution’s Perinatal Mood and Anxiety Disorders Program and staffed by the Psychiatry faculty. The clinic provides assessment and treatment, including both psychotherapy and medication for women with depression or anxiety disorders during pregnancy and the postpartum period. These cases were matched in 1:1 ratio to a random computer-generated referent group of 100 healthy women delivering at term (\( \geq 37 \) weeks) by race/ethnicity. The referent group included women with a documented negative Edinburgh Postnatal Depression Scale screening. Exclusion criteria for both cases and controls included medically indicated preterm delivery, multiple gestation, major congenital fetal anomalies, placenta previa, pre-eclampsia, pre-gestational hypertension, kidney disease, diabetes mellitus, known congenital or acquired thrombophilies, or any other significant pre-existing chronic medical disease. Furthermore, we excluded any women with a reported or diagnosed infection at the time of sample draw.

Serum levels of tumor necrosis factor-alpha (TNF-\( \alpha \)) were assayed in duplicate using Fluorokine MAP Human Base kits from R&I Systems per the manufacturer’s instructions. The intra- and inter-assay coefficients of variation were 4.2% and 6.8%, respectively. The mean minimum detectable dose for the TNF-\( \alpha \) assay was 0.60 pg/mL. Serum levels of interleukin (IL)-6 were assayed in duplicate using Quantikine HS IL-6 ELISA kits from R&I Systems per the manufacturer’s instructions. The intra- and inter-assay coefficients of variation were 7.4% and 7.8%, respectively. The mean minimum detectable dose for the ultrasensitive IL-6 assay was 0.04 pg/mL. Cytokine values were log transformed to normalize the data distribution prior to statistical analyses. IL-6 and TNF-\( \alpha \) refer to the log transformed value for these markers throughout. Data points \( \pm 3 \) standard deviations from the mean were considered to be outliers. Using this cut-off, none of the samples were
excluded from analyses. This study was run in parallel with our project estimating the association of Epstein–Barr virus reactivation with maternal depression in pregnancy.\textsuperscript{18} The samples were not accessed prior to our assays.

Data were analyzed using \textit{spss} statistics software (version 19.0) and were summarized using basic descriptive statistics. We performed the unadjusted analyses using Wilcoxon’s signed-rank and McNemar’s $\chi^2$ tests to compare differences between cases and controls. All $P$-values were two-tailed, with $P < 0.05$ considered statistically significant. Conditional logistic regression analyses, including previously identified covariates, were utilized to test the primary hypotheses related to relations between maternal depression and inflammatory markers.

### Results

We identified and analyzed 200 maternal serum samples (100 cases, 100 controls). The mean gestational age of serum collection was similar for both groups (12.6 vs 12.8 weeks). Maternal demographics, as presented in Table 1, only differed with respect to older age (34.1 vs 32.7 years, $P = 0.05$), and lower body mass index among depressed women (27.3 vs 28.9 kg/m$^2$, $P = 0.03$). Among the 100 women with depression, 66 were treated with anti-depressant pharmacotherapy, including 53 on selective serotonin reuptake inhibitors (SSRI)/serotonin-norepinephrine reuptake inhibitors, six on tricyclic antidepressants, two on atypical antidepressants (Trazodone and Bupropion), and five on combination therapy.

Compared to control women, TNF-$\alpha$ (5.8 ± 3.4 vs 3.2 ± 2.8 pg/ml, $P < 0.0001$) and IL-6 (2.4 ± 3.8 vs 1.5 ± 1.4 pg/ml, $P = 0.03$) levels were higher among women with depression (Figs 1, 2). The higher rate of inflammatory cytokines remained significant after controlling for potential confounders, including maternal age and body mass index. In order to remove confounding from race/ethnicity-related differences in cytokine levels, we compared only Caucasian women in each group and found that a higher rate of inflammatory cytokines remained significant in depressed women. Finally, we were not able to demonstrate an association between the class of antidepressants and cytokine levels.

*Table 1* Maternal demographics of study cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Depressed $n = 100$</th>
<th>Controls $n = 100$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>34.1 ± 4.6</td>
<td>32.7 ± 5.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>81</td>
<td>78</td>
<td>0.63</td>
</tr>
<tr>
<td>African-American</td>
<td>10</td>
<td>9</td>
<td>0.58</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7</td>
<td>9</td>
<td>0.72</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>4</td>
<td>0.26</td>
</tr>
<tr>
<td>Primiparous</td>
<td>43</td>
<td>46</td>
<td>0.78</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>27.3 ± 5.4</td>
<td>28.9 ± 4.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Public insurance (Medicaid)</td>
<td>16</td>
<td>12</td>
<td>0.27</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>11</td>
<td>8</td>
<td>0.46</td>
</tr>
<tr>
<td>Illicit substance abuse (cocaine, marijuana)</td>
<td>3</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Sexually transmitted infection</td>
<td>6</td>
<td>5</td>
<td>0.87</td>
</tr>
<tr>
<td>Gestational age at serum draw (weeks)</td>
<td>12.8 ± 1.2</td>
<td>12.6 ± 1.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Antidepressant medication use</td>
<td>66</td>
<td>0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or percentage; Wilcoxon’s signed-rank test and McNemar’s $\chi^2$ test were used for statistical analysis. SD, standard deviation.

*Figure 1* Log transformed tumor necrosis factor-$\alpha$ levels (pg/mL) in women with depression versus controls.
Discussion

In the present study, we tested the hypothesis that maternal depression is associated with a disproportionate pro-inflammatory state. Our results demonstrated higher levels of the pro-inflammatory cytokines in otherwise healthy women with a pre-pregnancy diagnosis of depression. This finding further supports our hypothesis that depression and related maternal stress may lead to a generalized pro-inflammatory state.

Recently, Christian et al. demonstrated an association between perceived maternal stress and depressive symptoms with higher circulating levels of pro-inflammatory cytokines.12 Our results confirm their findings as we also demonstrated elevated levels of TNF-α and IL-6 in our cohort of depressed women. More recently, Cassady-Bushrow et al. showed an association between depressive symptoms and inflammatory cytokines in a predominantly African-American urban cohort; however, such an association was not seen with TNF-α.13 In contrast, Blackmore et al. did not find such an association in their low-income, high-psychosocial-risk group of pregnant women.14 Nevertheless, these data underscore the need for large-scale projects prospectively examining various psychosocial variables in relation to circulating inflammatory cytokine levels. It must be noted that the relation between stress/depression and inflammatory cytokines is likely bi-directional. As summarized nicely in two recent reviews, Krishnadas and Haroon both point to the mounting evidence supporting the role of inflammatory mediators in the development of major depressive disorder and other neuropsychiatric illnesses. Indeed, inflammatory illnesses or treatment with cytokines render an elevated risk for development of depression, which further lends support to this theory.19,20

Our findings must be interpreted in the context of the study design. It is possible that this cross-sectional design fails to capture possible cytokine fluctuations later in the pregnancy, which would potentially affect our reported rates. Similarly, due to our study design, we were unable to control for the confounding introduced from the exact time of the blood draw in the day and therefore our data may be impacted by diurnal variations in cytokine levels. Given that our study utilized first-trimester genetic screening samples, we had a higher proportion of privately insured Caucasian women, and our results may not be generalizable to other more socioeconomically diverse populations. This may have led to lower rates of stress and inflammatory cytokines in both study groups. Furthermore, we cannot comment on other measures of stress, such as socioeconomic and psychosocial variables, because of the retrospective nature of our study. Further studies on heterogeneous populations that accrue data prospectively should be done to address these issues. Further, we did not prospectively evaluate controls for anxiety or depression, and thus some women in the ‘healthy’ group may have been misclassified. If this were the case, then their exclusion would potentially lead to an even larger difference between the study groups. Finally, there is mounting evidence that SSRI agents modulate anti-inflammatory cytokine production, at least in in vitro studies.21 In our population of depressed women treated with this class of agents, we were not able to demonstrate a significant difference based on the specific agent used; however, this may be a reflection of our smaller sample size.

In summary, we demonstrated higher levels of the pro-inflammatory cytokines in otherwise healthy women with a pre-pregnancy diagnosis of depression. Considering the mounting evidence linking a generalized pro-inflammatory state and stress, we believe that further examination of this association in pregnancy can address a gap in our knowledge of the causal pathway leading to adverse perinatal outcomes.

Disclosure

The authors have no financial relationships or conflicts of interest to disclose.

References


