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Effects of Stress and Depression on Inflammatory Immune Parameters in Pregnancy

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Abstract

There is a substantial body of literature linking psychological stress to adverse pregnancy outcomes, particularly preterm birth. Comparatively few studies have examined potential biological mechanisms explaining these associations. Attention to inflammatory processes is warranted. The current paper describes emerging studies demonstrating that, as in nonpregnant humans and animals, psychological stress and distress (i.e., depressive symptoms) predict dysregulation of inflammatory processes in human pregnancy. This includes elevations in circulating inflammatory cytokines, exaggerated inflammatory responses to *in vivo* biological challenges, and more robust inflammatory responses to psychological challenges. Continued research in this area is needed to determine the implications of such stress-induced immune dysregulation for birth outcomes as well as maternal health and fetal development.

Keywords

Inflammation; proinflammatory cytokines; psychological stress; depressive symptoms; psychoneuroimmunology

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1. Psychosocial Stress and Birth Outcomes

Stress measured in a variety of ways has been associated with increased risk of preterm birth after controlling for traditional risk factors in over three dozen studies. for review see [1, 2] This literature has become more consistent over time, reflecting more rigorous research methodology and larger sample sizes. Across studies, women reporting greater stress or distress exhibit 1.5–3 times greater risk of preterm delivery as compared to their less distressed counterparts. Supporting the conceptualization of minority status as a chronic stressor, perceived racial discrimination has repeatedly been linked to increased risk of preterm delivery and low birth weight. In addition, other subjective and objective indicators of stress are associated with increased risk of preterm delivery among African Americans as well as women of other races. These include perceived stress, general distress, occurrence of stressful life events, pregnancy-specific stress/anxiety, and depressive symptoms.

2. Biological Pathways Linking Stress and Health

Despite substantial literature linking psychological stress to adverse pregnancy outcomes, comparatively few studies have examined potential biological mechanisms explaining these associations and available studies have focused almost exclusively on potential neuroendocrine mediators. [e.g., 3, 4–6] Attention to inflammatory processes is warranted. In nonpregnant humans and animals, it is well-established that stress and distress (e.g., depressive symptoms) predict dysregulation of inflammatory processes including elevated circulating inflammatory cytokines, greater inflammatory responses to psychological stressors, and exaggerated inflammatory responses to *in vitro* and *in vivo* biological challenges.[7] The extent to which such effects generalize to pregnancy is not well delineated.

3. Stress and Inflammatory Processes Among Pregnant Women

Depressive Symptoms and Serum Inflammatory Markers

We examined psychosocial factors and serum proinflammatory cytokines among 60 pregnant women recruited from the OSU Prenatal Clinic, which serves a diverse and largely disadvantaged population. The majority of participants were African American (57%), had completed high school or less education (82%), and reported a total annual family income of less than $15,000 per year (63%). Women were assessed at one timepoint, primarily in the late first or early second trimester (15 ± 7.8 weeks gestation). Those with greater depressive symptoms, as measured by the Center for Epidemiological Studies Depression scale (CES-D), had higher levels of circulating IL-6 (β=.23, p=.05) and marginally higher TNF-α (β=.24, p=.06).[8] The magnitude of this effect was similar to that reported in nonpregnant adults. [e.g., 9] An effect for racial differences in IL-6 approached statistical significance ($t(49) = -1.6$, p =.12), with African American women exhibiting non-significantly higher levels. African American women did not differ significantly from White women in depressive symptoms, education, income, or number of previous pregnancies. These initial findings indicate that, as is well-documented in non-pregnancy, depressive symptoms are associated with elevations in circulating inflammatory markers during pregnancy. The translation of these findings to the prenatal period is notable because pregnancy is a time of significant immune adaptation and occurs in relatively young women.

Depressive Symptoms and Inflammatory Responses to an In Vivo Biological Challenge

In addition to associations with serum or circulating levels of inflammatory markers, stress can also alter immune responses to biological challenges. Moreover, because such challenges elicit a response, these models may have more predictive power than descriptive measures of circulating markers because they induce greater variability between subjects.

For clear ethical reasons, human studies of the inflammatory response system in pregnant women to-date have relied almost exclusively on *in vitro* models. [e.g.10, 11] Although highly useful, *in vitro* techniques involve isolation of specific cells, removal of cells from the complex *in vivo* environment, and exposure to higher levels of antigen than normally occurs *in vivo.*[12] By providing insight into immune function in the complex, multifaceted, naturally-occurring environment, *in vivo* models may provide data with clearer clinical relevance.

Vaccines have been used as a model to examine *in vivo* inflammatory responses in nonpregnant adults.[13–18] Greater inflammatory responses to vaccines have been reported among older adults with greater depressive symptoms [17] as well as men with carotid artery disease,[18] suggesting that responses to vaccination differ among those experiencing conditions with an inflammatory component. Seasonal influenza virus vaccination provides a novel model for examining inflammatory responses to an *in vivo* immune challenge among pregnant women, as this vaccination is currently recommended by the Centers for Disease Control (CDC) and American College of Obstetricians and Gynecologists (ACOG) for all women without contraindications who are pregnant or will be pregnant during flu season.[19, 20]

Using flu vaccine as an *in vivo* challenge model, we have demonstrated that psychosocial factors are associated with differential inflammatory responses in pregnant women. Twenty-two pregnant women were assessed prior to and approximately one week after vaccination.[21]. Compared to those in the lowest tertile of CES-D scores (n=8), those in the highest tertile (n=6) had significantly higher levels macrophage migration inhibitory factor (MIF) at one week post-vaccination. Groups did not differ in demographics (e.g., age, BMI, race, income) or health behaviors (e.g., sleep, smoking, regular exercise).

The absence of inflammatory response at one week post-vaccination among women with lower depressive symptoms is consistent with previous evidence that seasonal influenza virus vaccination does not generally cause an extended inflammatory response.[13, 17, 22] Thus, the extended inflammatory responses seen among the more depressed women are indicative of dysregulation of normal inflammatory processes. This study provides evidence that psychological stress predicts sensitization of inflammatory responses to an *in vivo* immune trigger during human pregnancy. If this represents a stable response tendency, women with this predisposition may show similarly exaggerated responses to everyday immune insults, resulting in a cumulative exposure to inflammatory mediators that is clinically meaningful with regard to perinatal health outcomes.

Racial Differences in Inflammatory Responses to Acute Psychological Stress

Differential physiological reactivity to acute stress is an important predictor of health outcomes in nonpregnant populations.[7, 23, 24] More than one dozen studies have examined cardiovascular and neuroendocrine reactivity to acute stress in pregnancy. Overall these data suggest that stress responses are attenuated during healthy pregnancy. [for review see 25, 26] Similar attenuation of responsivity has been reported in animal models.[27–29] These adaptations may be critical from protecting the mother and fetus from excessive exposure to physiological activation. However, data on inflammatory responses to stress during pregnancy are lacking.

We examined 39 women in the 2nd trimester of pregnancy (19 African American; 20 White) and 39 demographically similar nonpregnant women who completed an acute stressor (Trier Social Stress Test). Psychosocial characteristics, health behaviors, and affective responses were assessed. Serum interleukin(IL)-6 was measured via high sensitivity ELISA at baseline, 45 minutes, and 120 minutes post-stressor. Our results showed that IL-6 responses at 120 minutes post-stressor were 46% higher in African Americans versus Whites (95% CI: 8%–81%; $t(72) = 3.51$, $p = 0.001$). This effect was present in pregnancy and nonpregnancy. IL-6 responses at 120 minutes post-stressor tended to be lower (15%) in pregnant versus nonpregnant women (95% CI : −5%-32%; $p = 0.14$). Racial differences in inflammatory responses were not accounted for by demographics, psychological characteristics, health behaviors, or differences in salivary cortisol across the study session. Pregnant Whites also showed lower negative affective responses than nonpregnant women of either race ($ps \leq 0.007$).

This study provided novel evidence that stress-induced inflammatory responses are more robust among African American women versus Whites during pregnancy and nonpregnancy. This could be attributable to chronic stress associated with racial minority status. The ultimate impact of stress on health is a function of stressor exposure and physiological responses. Again, women who experience repeated and extended exposure to high levels of inflammatory mediators in response to psychological stressors may cumulatively experience a physiological burden which impacts perinatal health. Thus, individual differences in stress-induced inflammatory responses represent a clear target for continued research efforts in racial disparities in health during pregnancy and nonpregnancy.

4. Conclusions and Future Directions

In conclusion, these data support the notion that relationships between psychosocial stress and dysregulation of inflammatory processes that are well documented in nonpregnant adults are also present in pregnancy, despite significant immune adaptation that occur during this time. Specifically, our data show that psychological stress or distress (i.e., depressive symptoms) during pregnancy is associated with elevated serum inflammatory markers as well as exaggerated inflammatory responses to both biological and psychosocial challenges. Continued research in this area is needed to determine the implications of such stress-induced immune dysregulation for maternal health, fetal development, and birth outcomes.

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