SPECIAL REPORT

Effects of stress and depression on inflammatory immune parameters in pregnancy

Lisa M. Christian, PhD

There is a substantial body of literature that links psychological stress to adverse pregnancy outcomes, particularly preterm birth. Comparatively few studies have examined potential biologic mechanisms that explain these associations. Attention to inflammatory processes is warranted. This article describes emerging studies that demonstrate that, as in nonpregnant humans and animals, psychological stress and distress (ie, depressive symptoms) predict dysregulation of inflammatory processes in human pregnancy. This includes elevations in circulating inflammatory cytokines, exaggerated inflammatory responses to in vivo biologic 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 and for maternal health and fetal development.

Key words: inflammatory, proinflammatory cytokine, psychological stress, depressive symptom

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

Biologic pathways that link stress and health

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

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 who were recruited from the Ohio State University Prenatal Clinic, which serves a diverse and largely disadvantaged population. Most participants were African American (57%), had completed high school or less education (82%), and reported a total annual family income of <$15,000 per year (63%). Women were assessed at one time point, primarily in the late

From the Departments of Psychiatry, Psychology, and Obstetrics and Gynecology and the Institute for Behavioral Medicine Research, The Ohio State University Wexner Medical Center, Columbus, OH.

Received June 4, 2014; accepted June 17, 2014.

Manuscript preparation and the studies described were supported by National Institute of Nursing Research (R01 NR013661) and National Institute of Child Health and Human Development (R21 HD061644 and R21 HD067670). The studies described were also supported by Award Number Grant UL1TR000090 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. National Institutes of Health had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

The author reports no conflict of interest.

Corresponding author: Lisa M. Christian, PhD. Lisa.Christian@osumc.edu

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2014.06.042

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, had higher levels of circulating interleukin (IL)-6 ($\beta = .23$; $P = .05$) and marginally higher tumor necrosis factor−α ($\beta = .24$; $P = .06$).[8] The magnitude of this effect was similar to that reported in nonpregnant adults.[9] An effect for racial differences in IL-6 approached statistical significance ($t(49) = -1.6$; $P = .12$), with African American women exhibiting nonsignificantly 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 nonpregnancy, 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 biologic challenge

In addition to associations with serum or circulating levels of inflammatory markers, stress can also alter immune responses to biologic 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.[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] and men with carotid artery disease,[18] which suggests that responses to vaccination differ among those who experience conditions with an inflammatory component. Seasonal influenza virus vaccination provides a novel model for the examination of inflammatory responses to an in vivo immune challenge among pregnant women, because this vaccination currently is recommended by the Centers for Disease Control and American College of Obstetricians and Gynecologists 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 before and approximately 1 week after vaccination.[21] Compared with those in the lowest tertile of Center for Epidemiological Studies Depression scores (n = 8), those in the highest tertile (n = 6) had significantly higher levels of macrophage migration inhibitory factor at 1 week after vaccination. Groups did not differ in demographics (eg, age, body mass index, race, income) or health behaviors (eg, sleep, smoking, regular exercise).

The absence of inflammatory response at 1 week after vaccination among women with lower depressive symptoms is consistent with previous evidence that seasonal influenza virus vaccination generally does not cause an extended inflammatory response.[13,17,22] Thus, the extended inflammatory responses that are 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 that result in a cumulative exposure to inflammatory mediators that are 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 12 studies have examined cardiovascular and neuroendocrine reactivity to acute stress in pregnancy. Overall these data suggest that stress responses are attenuated during healthy pregnancy.[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 second trimester of pregnancy (19 African American women; 20 white women) and 39 demographically similar nonpregnant women who completed an acute stressor (Trier Social Stress Test).[30] Psychosocial characteristics, health behaviors, and affective responses were assessed. Serum IL-6 was measured with high sensitivity enzyme-linked immunosorbent assay at baseline, 45 minutes, and 120 minutes after the stressor. Our results showed that IL-6 responses at 120 minutes after the stressor were 46% higher in African American women vs white women (95% confidence interval, 8−81%; $t(72) = 3.51$; $P = .001$). This effect was present in pregnancy and nonpregnancy. IL-6 responses at 120 minutes after the stressor tended to be lower (15%) in pregnant vs nonpregnant women (95% confidence interval, −5 to 32%; $P = .14$). 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 white women also showed lower negative affective responses than nonpregnant women of either race ($P \leq .007$).

This study provided novel evidence that stress-induced inflammatory responses are more robust among African American women vs white women during pregnancy and nonpregnancy. This could be attributable to chronic stress that is associated with racial minority status. The ultimate impact of stress on health is a function of stressor exposure and physiologic responses. Again, women who experience repeated and extended exposure to high levels of inflammatory mediators in response to psychological stressors may experience cumulatively a physiologic burden that 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.

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 (ie, depressive symptoms) during pregnancy is associated with elevated serum inflammatory markers and exaggerated inflammatory responses to both biologic 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. ■

REFERENCES

1. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth: causes, consequences, and prevention Washington, DC: National Academies Press; 2007:89-123.
2. Christian LM. Psychoneuroimmunology in pregnancy: immune pathways linking stress with maternal health, adverse birth outcomes, and fetal development. Neurosci Biobehav Rev 2012;36:350-61.
3. Mancuso RA, Schetter CD, Rini CM, Roesch SC, Hobel CJ. Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. Psychosom Med 2004;66:762-9.
4. Kramer MS, Lydon J, Seguin L, et al. Stress pathways to spontaneous preterm birth: the role of stressors, psychological distress, and stress hormones. Am J Epidemiol 2009;169:1319-26.
5. Hobel CJ, Dunkel-Schetter C, Roesch SC, Castro LC, Arora CP. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. Am J Obstet Gynecol 1999;180(suppl):S257-63.
6. Wadhwa PD, Garite TJ, Porto M, et al. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol 2004;191:1063-9.
7. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 2004;130:601-30.
8. Christian LM, Franco A, Glaser R, Iams J. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain Behav Immun 2009;23:750-4.
9. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279-83.
10. Elenkov IJ, Wilder RL, Bakalov VK, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: Implications for autoimmune disease activity during these times. J Clin Endocrinol Metab 2001;86:4933-8.
11. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. Clin Exp Immunol 1996;106:127-33.
12. Vedhara K, Fox JD, Wang ECY. The measurement of stress-related immune dysfunction in psychoneuroimmunology. Neurosci Biobehav Rev 1999;23:699-715.
13. Posthouwer D, Voorbij HAM, Grobbee DE, Numans ME, van der Bom JG. Influenza and pneumococcal vaccination as a model to assess C-reactive protein response to mild inflammation. Vaccine 2004;23:362-5.
14. Hingorani AD, Cross J, Kharbanda RK, et al. Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation 2000;102:994-9.
15. Van der Beek MT, Visser LG, de Maat MPM. Yellow fever vaccination as a model to study the response to stimulation of the inflammation system. Vasc Pharmacol 2002;39:117-21.
16. Doherty JF, Golden MHN, Raynes JG, Griffin GE, Mcadam KPWJ. Acute-phase protein response is impaired in severely malnourished children. Clin Sci 1993;84:169-75.
17. Glaser R, Robles T, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses following influenza vaccination in older adults. Arch Gen Psychiatry 2003;60:1009-14.
18. Carty CL, Heagerty P, Nakayama K, et al. Inflammatory response after influenza vaccination in men with and without carotid artery disease. Atertioscler Thromb Vasc Biol 2006;26:2738-44.
19. American College of Obstetricians and Gynecologists. Influenza vaccination during pregnancy. Committe Opinion no. 468. Obstet Gynecol 2010;116:1006-7.
20. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. MMWR Morb Mortal Wkly Rep 2009;58:RR-8.
21. Christian LM, Franco A, Iams JD, Sheridan J, Glaser R. Depressive symptoms predict exaggerated inflammatory response to in vivo immune challenge during human pregnancy. Brain Behav Immun 2010;24:49-53.
22. Tsai M, Hanson N, Straka R, et al. Effect of influenza vaccine on markers of inflammation and lipid profile. J Lab Clin Med 2005;145:323-7.
23. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. Psychosom Med 2003;65:46-62.
24. McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 2008;583:174-85.
25. De Weerth C, Buitelaar JK. Physiological stress reactivity in human pregnancy: a review. Neurosci Biobehav Rev 2005;29:295-312.
26. Christian LM. Physiological reactivity to psychological stress in human pregnancy: Current knowledge and future directions. Prog Neurobiol 2012;99:106-16.
27. Rohde W, Ohkawa T, Dobashi K, Arai K, Okinaga S, Dorner G. Acute effects of maternal stress on fetal blood catecholamines and hypothalamic Lh-Rh content. Exp Clin Endocrinol 1983;82:268-74.
28. Neumann ID, Torner L, Wigger A. Brain oxytocin: differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. Neuroscience 2000;95:567-75.
29. Neumann ID, Johnstone HA, Hatzinger M, et al. Attenuated neuroendocrine responses to emotional and physical stressors in pregnant rats involve adenohypophyseal changes. J Physiol (Lond) 1998;508:289-300.
30. Christian LM, Glaser R, Porter K, Iams JD. Stress-induced inflammatory responses in women: Effects of race and pregnancy. Psychosomatic Medicine 2013;75:658-69.