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Stress and Immune Function during Pregnancy: An Emerging Focus in Mind-Body Medicine

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Abstract

Maternal psychosocial stress during pregnancy is associated with risks to maternal health, birth outcomes, as well as adverse health and behavioral outcomes in offspring. Maternal immune dysregulation, particularly disruption of inflammatory processes, is also implicated in adverse perinatal health outcomes, with the greatest evidence in relation to preterm birth. Increasingly, the extent to which psychosocial stress induces dysregulation of inflammatory processes during pregnancy is being considered. In this article, I describe studies linking stress to immune function during pregnancy, with an emphasis on studies from our group on inflammation. As will be reviewed, research utilizing psychoneuroimmunology models in pregnancy is a rapidly developing area with abundant opportunities to address questions of clinical relevance for both maternal and child health.

Keywords

Psychoneuroimmunology; Pregnancy; Stress; Immune; Perinatal

Stress and Health in Pregnancy

Maternal psychosocial stress during pregnancy is associated with risks for maternal health (e.g., gestational hypertension), birth outcomes (e.g., preterm birth), and adverse health outcomes in offspring (e.g., cognitive development) (Beydoun & Saftlas, 2008; Dunkel Schetter, 2011; Glover et al., 2010). Stress has been most commonly studied in association with birth outcomes. Demonstrating the magnitude of such effects, a meta-analysis of 29 studies concluded that depression during pregnancy poses a risk for preterm birth and low

birth weight comparable to smoking 10 cigarettes per day (Grote et al., 2010). Relationships between stress and preterm birth, as well as other perinatal health outcomes, generally remain after accounting for traditional behavioral risk factors, supporting a role for direct physiological links.

This review focuses on immune correlates of psychological stress during pregnancy, with an emphasis on studies from our group on inflammation. A variety of constructs have been examined across studies, including general perceived stress, pregnancy-specific stress, subjective distress (e.g., depression), and exposure to objective stressors (e.g., racial discrimination) (See Fig 1). Although conceptually distinct, for this article the term “stress” will be used in a comprehensive manner that includes these varied constructs. Of note, this review is not intended to be comprehensive. The reader is encouraged to refer to cited papers and suggested readings for additional depth in specific areas.

Emerging Evidence of Stress-Induced Inflammation in Pregnancy

It is clearly established that acute and chronic stress affects a variety of clinically meaningful immune parameters including wound healing, antibody responses to vaccines, susceptibility to infectious illnesses, the ability of the immune system to suppress latent viruses, as well as inflammatory processes (Coe, 2010). Importantly, the immune system undergoes substantial adaptations during pregnancy, and the literature linking stress and immune parameters, particularly inflammation, in the perinatal period is growing rapidly.

Inflammation plays a key role in response to infection or injury. Cytokine levels in the blood are frequently used as a measure of inflammation. Cytokines are proteins involved in communication between immune cells. In addition to their key role in inflammatory immune responses, cytokines also have broader effects, including effects on the brain which cause behavioral changes, such as fatigue, reduced appetite, and withdrawal, seen in response to illness (Dantzer & Kelley, 2007). Although critical in response to immune challenges, chronic or excessive inflammation is linked to negative health outcomes including cardiovascular diseases, diabetes, and some cancers.

Inflammation is modulated across the course of pregnancy. Both implantation and parturition are inflammatory events, at least at the local placental/uterine level, and these processes are carefully controlled (Mor et al., 2011). For clinical purposes, it would be of most utility to identify potentially detrimental dysregulation of immune processes at the peripheral level, via blood samples. Pregnancy is typified by elevations in circulating inflammatory mediators as compared to non-pregnancy, however, excessive inflammation or deviations in trajectories of change across pregnancy have been implicated in gestational hypertension, miscarriage, preterm birth and adverse effects on fetal development (for review see Christian, 2012b). Therefore, the role of stress in promoting inflammation in pregnancy is increasingly being considered.

Psychological stress and circulating inflammatory markers

In non-pregnant adults, psychological stress, defined in varied manners, has repeatedly been linked to elevations in circulating proinflammatory cytokines (Segerstrom & Miller, 2004).

Emerging studies from our group and others show that, despite substantial immune changes, similar effects are quantifiable during pregnancy.

In one of the first studies of this type, Coussons-Read and colleagues found that, among 24 pregnant women, greater perceived stress was associated with higher serum levels of interleukin (IL-6), tumor necrosis factor (TNF)- α , and lower levels of the antiinflammatory cytokine IL-10 (Coussons-Read et al., 2005). Subsequently, among 60 pregnant women, we observed no effects of perceived stress. However, higher depressive symptoms predicted elevations in serum levels of IL-6 and TNF- α (Christian et al., 2009). These effects were not accounted for by differences in smoking, prenatal vitamin use, exercise, or sleep, suggesting a role for direct physiological pathways linking depressive symptoms and inflammation. Similarly, in a study of 100 women with a diagnosis of clinical depression compared to a non-pregnant control group, Haeri and colleagues found that depressed women exhibited higher serum IL-6 and TNF- α (Haeri et al., 2013). Other data suggests that sleep disturbance and depression may interact to promote inflammation in pregnancy (Okun et al., 2013). In contrast, Blackmore et al., found that although depressive symptoms were not associated with inflammation, a history of trauma predicted elevations in TNF- α during pregnancy (Blackmore et al., 2011).

These studies indicate that pregnant women with particular psychological risk factors may experience higher daily exposure to inflammatory mediators. However, contrasting results are seen with regard to which psychological constructs are related to inflammation. Differing results may be attributable, in part, to differences in study samples. For example, our study focused on women from highly disadvantaged socioeconomic backgrounds with a high prevalence of clinically significant depressive symptoms. In this context, depressive symptoms may have greater predictive value than general perceived stress.

Obesity as a principal driver of inflammation

More than 1/3 of women in the US are obese, and more than 1/2 of pregnant women are overweight or obese (ACOG, 2013). Because adipocytes (fat cells) secrete proinflammatory cytokines, obesity is a primary driver of inflammation. Obesity can be conceptualized as a physiological stressor. Perinatal obesity increases risk of gestational hypertension and gestational diabetes via inflammatory pathways. Moreover, obesity-induced inflammation is transmitted to the child, potentially affecting their immune functioning, metabolism, and cognitive development (e.g., Bilbo & Tsang, 2010).

While showing a similar trajectory (i.e., slope) of change, obese women exhibit considerable elevations in circulating inflammatory markers, particularly IL-6, across pregnancy and postpartum (Christian & Porter, in press). Obesity should be considered as a potential causal pathway in the relationship between stress and inflammation (Fig 1). In addition, obesity and psychological stress may interact in a synergistic manner, resulting in more marked effects among women with both risk factors. Conversely, by inducing an inflammatory state, obesity may create a ceiling whereby psychological stress cannot exert a measurable additional effect. Demonstrating the latter, among 187 pregnant African American women, higher depressive symptoms predicted elevated serum IL-6 only among lean women while IL-6 was elevated in heavier women regardless of depressive status (Cassidy-Bushrow et al.,

2012). Thus, given the high prevalence, effects of obesity should be considered in psychological stress studies.

Self-rated health as an indicator of inflammatory status

As described, inflammation may promote symptoms of depression through sickness behaviors (i.e., fatigue, reduced appetite, social withdrawal). Along a similar vein, inflammation may affect general self-rated health (Christian et al., 2011). Of note, in non-pregnant adults, a large literature links a simple single-item measure of self-rated health to morbidity and mortality after accounting for various objective health indicators (Benyamini, 2011). Inflammation may contribute to this effect by influencing self-rated health prior to the emergence of objective and quantifiable signs of disease.

To determine if self-rated health provides information about inflammatory status in pregnancy, we examined 101 pregnant women in the 2nd trimester. We found that poorer self-rated health was associated with significantly higher serum IL-1 β and macrophage migration inhibitory factor (MIF) (Christian, Iams, et al., 2013). These associations were not fully accounted for by behavioral mediators including psychological stress, health diagnoses, BMI, or smoking. Thus, as seen in non-pregnant adults, self-rated health may provide insight into inflammatory status in pregnant women. The extent to which self-rated health corresponds to risk for adverse perinatal health outcomes remains to be determined.

Stress and inflammatory responses to biological immune challenges

The studies reviewed thus far have focused on levels of circulating inflammatory markers. Importantly, the immune system is dynamic, responding to both biological and psychological challenges. Individuals differ in their immune responses to such challenges, and these individual differences can be linked, in part, to psychological factors (Coe, 2010; Segerstrom & Miller, 2004). Compared to assessment of circulating markers, challenge models produce a broader range in the outcomes being measured, and thus may provide a stronger signal of atypical functioning.

Although elevations in circulating proinflammatory cytokines are observed in normal pregnancy, inflammatory responses to immune stimuli, such as bacteria and viruses, appear to be attenuated as compared to non-pregnancy (Denney et al., 2011). Stress may counteract this adaptation, priming women to show exaggerated responses compared to their less stressed counterparts.

For clear ethical reasons, such studies have focused almost exclusively on in vitro stimulation models. Such models demonstrate that stress affects response patterns. For example, among 17 women in the 3rd trimester, greater subjective stress predicted exaggerated production of both IL-1 β and IL-6 by lymphocytes stimulated in vitro (Coussons-Read et al., 2007). 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. In contrast, while less controlled, in vivo models provide insight into immune responses in the naturally-occurring neuroendocrine and immune environment of the body. Because it is safe and recommended for pregnant women, seasonal influenza

virus vaccination (the flu shot) provides a unique opportunity to study in vivo inflammatory responses in pregnancy.

The flu shot induces a mild and transient inflammatory response that is highly similar in pregnant and non-pregnant women (Christian, Porter, et al., 2013). Our data suggest that depressive symptoms may be linked to a propensity for exaggerated inflammatory responses to this immune challenge. Specifically, among 22 pregnant women, those in the highest tertile of depressive symptoms showed markedly higher inflammatory responses, as indicated by serum levels of macrophage migration inhibitory factor (MIF) at one week post-vaccination (Christian et al., 2010). If these in vitro and in vivo studies represent typical functioning, women with greater psychological stress may respond to everyday immune threats in an exaggerated manner, resulting in a considerably greater cumulative inflammatory burden across the course of pregnancy.

Inflammatory responses to acute psychological stress

We have also examined how inflammatory responses to psychological stress adapt during pregnancy, and the potential effects of chronic stress on such adaptation. Numerous studies have examined cortisol, catecholamine, and/or blood pressure responses to acute stress during pregnancy. Overall, healthy pregnant women appear to exhibit attenuated stress reactivity (Christian, 2012a; de Weerth & Buitelaar, 2005). These adaptations may serve a protective function, preventing the mother and fetus from excessive exposure to stress hormones and alterations in cardiovascular parameters including uterine blood flow.

Drawing upon this literature, we examined 1) whether inflammatory responses to acute stress are similarly attenuated during pregnancy compared to non-pregnancy and 2) whether African American women show differences in such adaptation. Our interest in possible racial differences was driven by the theory that inflammatory pathways related to chronic stress may contribute to the marked and persistent racial disparity in preterm birth (for review see Giscombe & Lobel, 2005).

To address these questions, we assessed 39 women in the 2nd trimester of pregnancy (19 African American and 20 White) and 39 demographically similar non-pregnant women who completed an acute stressor involving a mock job interview and mental arithmetic (Trier Social Stress Test). Serum samples were obtained repeatedly. Consistent with a dampening hypothesis, pregnant women exhibited 15% lower IL-6 responses to the stressor (Christian, Glaser, et al., 2013). In addition, significant effects of race were observed; during pregnancy and non-pregnancy African American women showed 46% higher IL-6 responses compared to Whites (Fig 2). These data highlight the importance of considering not only the frequency of exposure to stressors, but also the magnitude of physiological responses to these exposures, as responses to the same stressor can vary considerably between individuals.

Stress and Viral Latency

As reviewed, inflammation has been the central focus of studies of stress-induced immune dysregulation in pregnancy. However, viral latency also warrants attention. After initial infection, some viruses remain within cells in a dormant state known as latency. Epstein-

Barr virus (EBV), one of the most prevalent, is carried by more than 95% of US adults. EBV reactivation indicates that the cellular immune system is not optimally suppressing the virus. EBV reactivation causes few or no symptoms in healthy non-pregnant adults. However, in pregnancy some data links it to stillbirth, birth defects, shorter gestation, and lower birth weight (e.g., Eskild et al., 2005). Importantly, available studies cannot determine if EBV reactivation plays a causal role in such adverse outcomes. It is possible that, instead, impaired cellular immune competence is a causal driver.

Numerous studies have demonstrated that psychological stress can encourage reactivation of latent viruses, including EBV (e.g., Glaser et al., 1985). In pregnant women, greater EBV reactivation has been observed in association with maternal depression, perceived stress and perceived racial discrimination (Borders et al., 2010; Haeri et al., 2011). We examined 56 women (38 African American and 18 White) at each trimester of pregnancy and postpartum. Consistent with other studies, we found that African American women exhibited greater EBV reactivation than Whites at every timepoint, as indicated by higher serum levels of EBV capsid antigen immunoglobulin G (VCA IgG) antibody titers (Christian et al., 2012). Notably, this effect was significantly stronger among African American women who reported greater racial discrimination. Thus, our results and others' indicate that EBV reactivation may serve as a marker of stress-induced immune dysregulation during pregnancy.

Notably, one pathway by which viral reactivation may affect health is by promoting inflammation. However inflammation associated with viral reactivation may only be detectable in the context of reactivation of multiple viruses (Bennett et al., 2012). Thus, in future studies, assessment of multiple viruses as well as related inflammatory processes would be informative.

Bringing it all together: Stress, immune function, and perinatal health

This review has focused on growing data linking stress to immune dysregulation during pregnancy, particularly inflammatory processes. An ultimate goal of this body of research is to quantify the impact of such immune-dysregulation on specific perinatal health outcomes, and ideally, develop targeted interventions. To-date, studies in pregnancy have focused largely on demonstrating and quantifying the impact of stress on immune function. Very limited data have linked stress, inflammation, and perinatal health within the same study. One study supports a mediational role for inflammation in the link from pregnancy-specific anxiety and gestational age at delivery (Coussons-Read et al., 2012). Additional work demonstrating such mediational effects is clearly needed, with an expansion beyond the outcome of preterm birth.

Importantly, although beyond the scope of this review, effects of stress on immune processes are largely mediated by the neuroendocrine system (Ader, 2007). An extensive literature has examined stress and neuroendocrine function in pregnancy (for review see Dunkel Schetter, 2011; Entringer et al., 2010; Glynn et al., 2013; Hobel et al., 2008). Thus, greater integration of the literatures on neuroendocrine and immune parameters is an important future direction.

In addition to inflammation and viral latency, other immune outcomes that are known to be affected by stress and have relevance to perinatal health warrant greater attention. These include antibody responses to vaccines, wound healing, and the composition of the gut microbiome in both mothers and offspring. Research on stress-induced immune dysregulation in pregnancy represents a rapidly developing area of investigation which will continue to grow in breadth as well as integration with other literatures. As such, this presents abundant opportunities to address questions of clinical relevance for maternal and child health.

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Recommended Readings

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Figure 1. Pathways Linking Stress, Immune Function, and Perinatal Health Outcomes

Greater exposure to objectively stressful events results in greater experience of subjective distress (A). This effect is moderated by coping resources, including social support (B). Psychological distress may affect immune function via health behaviors (C) and direct physiological pathways (D) via effects on neuroendocrine and the sympathetic nervous system. In turn, immune parameters may affect maternal health (e.g., preeclampsia, susceptibility to infectious illness, wound healing), birth outcomes, and fetal development (E). *Reprinted from* Christian, L.M. (2012) *Psychoneuroimmunology in Pregnancy: Immune Pathways Linking Stress with Maternal Health, Adverse Birth Outcomes, and Fetal Development*. *Neuroscience and Biobehavioral Reviews*, 36, 350-361 with permission from Elsevier.

Fig 2. Inflammatory Responses to the Trier Social Stress Test in Pregnant and Nonpregnant Women

Controlling for baseline, IL-6 levels at 120 minutes post-stressor were 46% higher in African Americans versus Whites (95% CI: 18% to 81%; $t(72) = 3.51$, $p = .001$). This effect of race was significant during pregnancy and non-pregnancy. *Reprinted from Christian, L.M., Glaser, R., Porter, K & Iams, J.D. (2013). Stress-induced inflammatory responses in women: Effects of race and pregnancy. Psychosomatic Medicine, 75, 658-669.*