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Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy

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Abstract

Previous work has shown that psychosocial stress is related to increases in serum levels of pro-inflammatory cytokines late in pregnancy, and a growing body of research suggests that increased inflammatory activity during pregnancy, generally, may have a negative impact on outcome. The present study further addressed these issues by assessing relationships between psychosocial stress, social support and serum cytokines in early, mid, and late pregnancy, and the effects of stress and social support on the production of cytokines by stimulated lymphocytes in late pregnancy. In addition, we examined relationships between stress, support, and serum C-reactive protein (CRP) during pregnancy. Elevated stress was not only related to higher serum IL-6 late in pregnancy as in our prior work, but this relationship was also evident during early pregnancy, and elevated stress was also associated with lower IL-10 in early pregnancy. No relationships between stress and cytokines were apparent during the 2nd trimester of pregnancy. Elevated stress during the 2nd trimesters and low social support during the 3rd trimester were related to increased serum levels of CRP, further suggesting that psychosocial factors can contribute increased inflammation during pregnancy. Importantly, elevated stress levels across pregnancy were predictive of elevated production of the pro-inflammatory cytokines IL-1B and IL-6 by stimulated lymphocytes in the 3rd trimester, suggesting that stress during pregnancy affects the function of immune system cells. These findings further support the notion that prenatal stress alters maternal physiology and immune function in a manner consistent with increased risk of pregnancy complications such as preeclampsia and premature labor.

Keywords: Pregnancy; Stress; Cytokines; Lymphocytes; C-reactive protein; Human

1. Introduction

A growing body of data suggests that psychosocial factors such as high stress and low social support can negatively affect pregnancy success. Work in our laboratory and others has shown that women experiencing high levels of stress during pregnancy have increased levels of pro-inflammatory cytokines in the circulation compared to women who do not report high levels of prenatal stress (Ruiz et al., 2003; Coussons-Read et al., 2005). This is a potentially important change, since increased levels of pro-inflammatory cytokines and decreased amounts of anti-inflammatory cytokines have been associated with the occurrence of preeclampsia and premature labor (Piccinni et al., 2000). Although the existing literature provides some evidence that stress alters cytokine balance in a manner that may endanger pregnancy, these studies have been limited to assessments of serum levels of cytokines and lack longitudinal analysis of changes in cytokine balance across pregnancy. Increases in C-reactive protein (CRP), another inflammatory marker, have been implicated in the development of preeclampsia and premature labor, but no published studies have explored if they too are elevated by stress during pregnancy (Ruiz et al., 2003). The present study addressed relationships between psychosocial variables and serum inflammatory markers across pregnancy

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and began to directly address potential stress-related immune dysregulation during pregnancy by looking at production of cytokines by lymphocytes.

As in previous work, we utilized a psychoneuroimmunological framework to test the hypothesis that elevated stress during pregnancy increases levels of circulating inflammatory mediators and increases production of pro-inflammatory cytokines by lymphocytes during pregnancy (Coussons-Read et al., 2003; Coussons-Read et al., 2005). We have operationally defined stress as events, situations, emotions, and interactions which negatively affect the well being of the individual or which cause responses perceived as harmful, and psychosocial stressors include life experiences, such as changes in personal life, job status, housing, domestic violence, and family makeup, which require coping behavior on the part of the affected individual (Orr et al., 1992). Maternal stress experiences in pregnancy can range from severe and acute (e.g., trauma) to moderate (e.g., life event changes) to chronic (e.g., experience of daily hassles), and moreover, the state of pregnancy can affect how a woman views negative life events which may influence how she responds to stressors throughout pregnancy (Glynn et al., 2004). Although a few studies have shown little effect of prenatal stress on pregnancy (Dole et al., 2003), the majority of studies indicate that stress during gestation can contribute to poor pregnancy complications including recurrent spontaneous abortion, preeclampsia, and prematurity (i.e., Austin and Leader, 2000). These are important observations, as other studies have shown that infants of stressed pregnancies have higher rates of childhood illnesses and may experience physical and cognitive developmental delays (Cannon, 1998; Kang and Fox, 2000). Ongoing research addresses the mechanisms through which stress affects pregnancy outcome, and it has been suggested that changes in immune function resulting from stress may affect pregnancy. Stress reliably suppresses immune function in non-pregnant animals and humans, and stress exacerbates illnesses and infections (i.e., Rabin et al., 1990; Cohen et al., 1999), and some have suggested that stress-related changes in immune status may be involved in the deleterious effects of stress on pregnancy.

The immune system plays an important supporting role in pregnancy, and cytokines, produced by cells of the immune system during stress and infections, are involved in both the maintenance of pregnancy and onset of labor (Elenkov and Chouros, 1999). The maternal immune system must shift somewhat to accommodate healthy pregnancy, as the pregnant woman's immune system must be altered from its normal state to avoid rejection of the conceptus (Pope et al., 1983; Gennaro and Fehder, 1996). Changes in the pregnant immune system to avoid this include separation of maternal and fetal circulation, protection of the pregnant uterus as an immunologically privileged location, and changes in maternal lymphocyte function and subsets (Gennaro and Fehder, 1996). In addition, the pregnant woman's immune system appears to shift away from inflammatory immune responses to favor more anti-inflammatory responses (i.e., Reinhard et al., 1998). Some support for this assertion comes from studies showing that pro- and anti-inflammatory cytokines produced by cells of the immune system are involved in maintenance of pregnancy, labor and delivery, and in some cases, pregnancy complications. For example, pro-inflammatory cytokines are involved in the ripening of the cervix before delivery, and elevated levels of IL-6, IL-8, and TNF-α are associated with premature labor and delivery (Zhang et al., 2000). Similarly, infections contribute to premature labor and delivery, and cytokines produced as part these infections may play a role in prematurity (Gomez et al., 1995). Thus, although pro-inflammatory cytokines support the immune response to infection, they can also contribute to preterm labor and delivery if overproduced. In addition, serum levels of the anti-inflammatory cytokine IL-10 are significantly higher in successful pregnancies than in miscarriages, and low placental IL-10 has been associated with development of preeclampsia, further suggesting that a shift away from an inflammatory profile may facilitate pregnancy completion (Lim et al., 1999; Hennessy et al., 1999; Jenkins et al., 2000; Piccinni et al., 2000). Together, these studies indicate that successful pregnancy may depend, in part, on a relative reduction in production of pro-inflammatory cytokines compared to anti-inflammatory cytokines, and thus, the present study focused on assessments IL-6, IL-1B, TNF-α, and IL-10.

Other inflammatory markers have been implicated in pregnancy complications, suggesting that increased inflammation beyond what is normal during pregnancy is related to pregnancy complications (Ruiz et al., 2003). For example, elevations in serum levels of CRP, an inflammatory mediator produced in the liver and a maker of systemic inflammation are associated with increased risk of developing preeclampsia and gestational diabetes (Reron et al., 2004). Stress increases levels of CRP in the serum of non-pregnant adults, but no published studies have determined if stress during pregnancy elevates maternal CRP in a manner which may be deleterious to pregnancy outcome (Oparil and Oberman, 1999; Jeanmonod et al., 2004). The present study incorporated assessments of serum CRP across pregnancy to begin to address this question.

Our previous work showed that high psychological stress and low social support during pregnancy predict elevated serum pro-inflammatory cytokines, raising the possibility that stress-related increases in pro-inflammatory cytokines may increase occurrence of poor pregnancy outcomes, specifically premature labor and the development of preeclampsia. Much of the existing literature on the effects of cytokines during pregnancy relies on levels of serum cytokines measured via enzyme-linked immunosorbent assays (ELISA). Although serum data are useful in beginning to understand the effects of stress on inflammatory mediators during pregnancy, they do not provide any direct evidence that the immune system is being affected by stress during pregnancy. Serum cytokine levels may not only reflect immune cell activity in the blood and lymphoid