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# Immune dysregulation and glucocorticoid resistance in minority and low income pregnant women

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**Summary** Chronic prenatal stress contributes to poor birth outcomes for women and infants. Importantly, poor birth outcomes are most common among minority and low income women. To investigate underlying mechanisms, we tested the hypothesis that chronic stress related to minority or low income status is associated with glucocorticoid resistance as indicated by disruption in the cytokine-glucocorticoid feedback circuit. Home visits were conducted during which 3rd trimester pregnant women completed stress and depression surveys and provided blood for pro- and anti-inflammatory cytokines. Saliva was collected 5 times the preceding day for diurnal cortisol levels. For statistical analyses, women were grouped 3 ways, by race, income, and the presence or absence of either of those risk factors; this last group was labeled high or low general risk. Immune regulation was evaluated by evidence of a functioning negative feedback relationship between cytokines and cortisol. Of 96 participants, 18 were minority, 22 of low income, and 29 either minority or low income (high general risk). Pearson partial correlation identified a significant negative relationship between cortisol area under the curve (AUC) and pro- to anti-inflammatory cytokine ratios in the low general risk women (i.e., Caucasian, higher income) including IFN$\gamma$/IL10 ($r = -0.73$, $p < 0.0001$), IL6/IL10 ($r = -0.38$, $p = 0.01$), IL1$\beta$/IL10 ($r = -0.44$, $p = 0.004$) and TNF$\alpha$/IL10 ($r = -0.41$; $p = 0.005$); no such correlations existed in the high general risk women (i.e., minority, low income) for (IFN$\gamma$/IL10: $r = -0.25$, $p = 0.43$; IL6/IL10:

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$r = 0.12$, $p = 0.70$; IL1 β/IL10: $r = 0.05$, $p = 0.87$; TNFα/IL10: $r = 0.10$; $p = 0.75$), suggestive of glucocorticoid resistance. Cortisol levels throughout the day also were higher in minority and high general risk groups ($p < 0.05$). Without cytokine glucocorticoid feedback, a pregnant woman's ability to regulate inflammation is limited, potentially contributing to adverse maternal and infant outcomes.


Chronic prenatal stress contributes to adverse perinatal outcomes, including preterm birth (Institute of Medicine, 2007), intrauterine growth retardation (Nordentoft et al., 1996), and spontaneous miscarriage (Institute of Medicine, 2007). Infants born premature may experience mental and physical disabilities that last a lifetime (Calkins and Devaskar, 2011). Even infants born at or near term whose mothers were exposed to prenatal stress have increased risk of abnormal neurological development (Davis et al., 2011; Talge et al., 2007), infectious disease (Tegethoff et al., 2011), congenital malformation (Tegethoff et al., 2011), poor executive functioning (Buss et al., 2011), and mood or behavioral disturbance (Wadhwa, 2005). Although progress has been made to clarify key mechanisms underlying the associations between prenatal stress and adverse pregnancy outcomes (Karrow, 2006; Meaney et al., 2007; Sandman et al., 2011; Weaver, 2007), additional research is required to determine how perturbations in stress-related biological responses conspire to influence poor birth outcomes in high-risk populations (Kramer et al., 2011)

With mental or physical stress, a complex neuroendocrine-immune response is initiated (Sapolsky et al., 2000) that includes activation of the hypothalamic-pituitary-adrenal (HPA) axis and stimulation of the innate immune response, leading to the increased release of pro-inflammatory cytokines (Steptoe et al., 2007; Yang and Glaser, 2002). This response carries benefits as well as risks for a pregnant woman and her offspring. Acute inflammation offers protection from infection and supports healing. However, even acute inflammation increases the risk of premature delivery (Romero et al., 2006) while chronic inflammation carries additional complications, including gestational hypertension (Freeman et al., 2004) and diabetes (Richardson and Carpenter, 2007). Fetal exposure to prenatal inflammation is also under investigation for contributions to fetal growth restriction (Almasry et al., 2012) and childhood diagnosis of autism (Angelidou et al., 2012). Finally, pro-inflammatory cytokines are associated with sickness symptoms, that include fatigue, decreased sleep, poor cognitive function, and depressed mood (Dantzer and Kelley, 2007), each having the potential to impact maternal health.

Mechanisms are in place, during pregnancy (Elenkov et al., 2001) and at other times, to regulate inflammation including a key cytokine-glucocorticoid negative feedback circuit (Besedovsky and del Rey, 2006; Elenkov et al., 2005). Pro-inflammatory cytokines are potent activators of the hypothalamic-pituitary-adrenal (HPA) axis, and contribute to stress-induced elevation in cortisol secretion. Cortisol in turn, is not only important in mobilizing resources to respond to the stressor, but also plays a fundamental role in limiting the inflammatory response and the further production of cytokines (Anisman and Merali, 2003; Besedovsky and del Rey, 2006; Yang and Glaser, 2002). This occurs through synergistic, organized mechanisms (Pace and Miller, 2009), initiated by cortisol binding to glucocorticoid receptors present on immune cells that are critical for regulation of the inflammatory response, such as monocytes and lymphocytes. Considerable evidence suggests that activation of the glucocorticoid receptor attenuates activity of inflammatory signaling pathways, including those that promote production of pro-inflammatory cytokines, while activating pathways that promote production of anti-inflammatory cytokines.

In the case of chronic stress, it has been suggested that prolonged activation of the stress response can promote a state of glucococorticoid resistance that involves an inability of cortisol to inhibit pro-inflammatory signaling pathways, leading to a loss of the normal negative association between cortisol concentration and various indicators of inflammatory immune activation (Pace et al., 2007; Stark et al., 2001). For example, the negative correlation between plasma cortisol concentration and circulating leukocyte subsets seen in non-stressed individuals was lost in subjects experiencing a major chronic stressor during the preceding year, a finding identified as consistent with glucocorticoid resistance (Cohen et al., 2012). Among the mechanisms hypothesized for glucocorticoid resistance include the impact of stress-induced pro-inflammatory cytokine production on glucocorticoid receptor function (Engler et al., 2008; Raison and Miller, 2003) and that sustained elevations in cortisol in response to chronic stress lead to functional resistance to GR signal transduction (Miller et al., 2008). Ultimately, pro-inflammatory cytokine production can become dysregulated regardless of cortisol levels. Glucocorticoid resistance in response to chronic stress has been identified in caregivers of persons with cancer (Miller et al., 2008), parents of children with cancer (Miller et al., 2002), adults with a history of low early-life social class (Miller et al., 2009), and in women suffering post-traumatic stress syndrome (Pace et al., 2012a).

Although most research on stress and inflammation has focused on non-pregnant individuals, Coussons-Read et al. (2005), in a study of twenty-six pregnant women, reported a positive correlation between self-reported stress and maternal serum levels of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor-necrosis factor-alpha (TNF-α), and a negative correlation between stress and the anti-inflammatory cytokine interleukin-10 (IL-10). These findings suggested a mechanism by which chronic prenatal stress could be linked to adverse pregnancy outcomes. Subsequent reports by the same researchers furthered these findings (Coussons-Read et al., 2007), including most recently a report identifying a linkage between elevated serum cytokines and preterm birth (Coussons-Read et al., 2012). Others, however, have not confirmed a linkage between prenatal stress and either