Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression

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ABSTRACT

More than 500,000 U.S. women develop postpartum depression (PPD) annually. Although psychosocial risks are known, the underlying biology remains unclear. Dysregulation of the immune inflammatory response and the hypothalamic–pituitary–adrenal (HPA) axis are associated with depression in other populations. While significant research on the contribution of these systems to the development of PPD has been conducted, results have been inconclusive. This is partly because few studies have focused on whether disruption in the bidirectional and dynamic interaction between the inflammatory response and the HPA axis together influence PPD. In this study, we tested the hypothesis that disruption in the inflammatory-HPA axis bidirectional relationship would increase the risk of PPD. Plasma pro- and anti-inflammatory cytokines were measured in women during the 3rd trimester of pregnancy and on Days 7 and 14, and Months 1, 2, 3, and 6 after childbirth. Saliva was collected 5 times the day preceding blood draws for determination of cortisol area under the curve (AUC) and depressive symptoms were measured using the Edinburgh Postpartum Depression Survey (EPDS). Of the 152 women who completed the EPDS, 18% were depressed according to EDPS criteria within the 6 months postpartum. Cortisol AUC was higher in symptomatic women on Day 14 ($p = .017$). To consider the combined effects of cytokines and cortisol on predicting symptoms of PPD, a multiple logistic regression model was developed that included predictors identified in bivariate analyses to have an effect on depressive symptoms. Results indicated that family history of depression, day 14 cortisol AUC, and the day 14 IL8/IL10 ratio were significant predictors of PPD symptoms. One unit increase each in the IL8/IL10 ratio and cortisol AUC resulted in 1.50 ($p = 0.06$) and 2.16 ($p = 0.02$) fold increases respectively in the development of PPD. Overall, this model correctly classified 84.2% of individuals in their respective groups. Findings suggest that variability in the complex interaction between the inflammatory response and the HPA axis influence the risk of PPD.

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1. Introduction

Postpartum depression (PPD) is a major mood disorder (Association, 2013), affecting between 12% and 20% of new mothers (Gavin et al., 2005; Wisner et al., 2010). PPD is characterized by persistent fatigue, sadness, and anxiety (Beck, 2006; Corwin et al., 2005; Hay et al., 2008) and carries significant and lifelong health consequences for women and their infants (Field, 2010). These consequences may be intergenerational, as infants born to mothers with PPD grow up to be at an increased risk of developing a mood disorder themselves (Hay et al., 2008; Pearson et al., 2013). Although psychosocial risk factors for PPD have long been considered, a growing appreciation of the mind–body connection in health and disease has led to an increased focus on biological risk factors that may underlie or contribute to the disorder. Two biological systems that have come under investigation as potential contributors to PPD are the immune-inflammatory response (Anderson and Maes, 2013; Boufidou et al., 2009; Corwin et al., 2008; Groer and Morgan, 2007; Maes et al., 2000; Okun et al., 2011; Osborne and Monk, 2013) and the hypothalamic–pituitary–adrenal (HPA) axis (Glynn et al., 2013; O'Keane et al., 2011; Okun et al., 2011). Both undergo significant changes during pregnancy (Kalantaridou et al., 2010; Mastorakos and Ilias, 2003;

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Mor and Cardenas, 2010) and both remain in flux during the early postpartum period (Christian and Porter, 2014; Hebisch et al., 2004; Mastorakos and Ilias, 2003).

While not an immunosuppressive state (Mor and Cardenas, 2010), for most of pregnancy there is a shift away from a pro-inflammatory and toward an anti-inflammatory milieu in the mother, protecting the fetus from rejection (Aagaard-Tillery et al., 2006). However, by the end of the 3rd trimester, a pro-inflammatory milieu again emerges (Maes et al., 2000; Mor and Cardenas, 2010), playing an important role in the onset of parturition (Christiaens et al., 2008). This pro-inflammatory response accelerates during labor, as most women experience some degree of pain, anxiety, stress, and fatigue during that time, each of which serves as a stimulus for the secretion of pro-inflammatory cytokines (Steptoe et al., 2007; Watkins et al., 1999). The inflammatory response continues into the postpartum period as both pro- and anti-inflammatory mediators drive perineal healing and uterine involution as well as mammary involution in women who chose to bottle feed (Chapwanya et al., 2012; Hojilla et al., 2011; Nilsen-Hamilton et al., 2003; Salamonsen, 2003). Given the association between inflammation and depression in non-pregnant, non-postpartum populations (Dantzer and Kelley, 2007; Raison and Miller, 2013), more than a dozen research studies over the past two decades have considered exaggerated postpartum inflammation as a risk factor for PPD. A recent literature review, however, concluded that findings are inconsistent and do not allow for conclusions or generalizations to be made (Osborne and Monk, 2013). Limitations of prior studies include small sample sizes, inclusion of women with birth complications, limited reliability or validity of measures used to evaluate depression, and samples collected at a single time, or at inconsistent times, after delivery. In addition, very few studies have addressed the biological complexity of the psychoneuroimmune (PNI) response, specifically, the bidirectional and dynamic interaction between the inflammatory response and the HPA axis.

Like the immune system, the HPA axis is altered during pregnancy; by the second trimester maternal levels of serum cortisol are nearly double compared to levels seen in the non-pregnant state (Mastorakos and Ilias, 2003). Key to this scenario is the increased production of corticotropin-releasing hormone (CRH) by the placenta and fetal membranes as pregnancy advances; the resultant increase in cortisol production from these sources is resistant to negative feedback, although suppression of maternal hypothalamic CRH in response to the high levels of circulating cortisol is intact (Kalantaridou et al., 2010). With delivery of the infant and expulsion of the placenta, maternal cortisol levels fall significantly and quickly, to within the upper normal range (Chrousos et al., 1998). Maternal postpartum CRH suppression, however, has been hypothesized to continue for a variable period of time (Kalantaridou et al., 2010; Mastorakos and Ilias, 2003; Vitoratos et al., 2006). A growing body of evidence suggests that the abrupt fall in cortisol levels and postpartum HPA axis suppression contribute to postpartum mood disorders (Bloch et al., 2005; Chrousos et al., 1998; Glynn et al., 2013; Kalantaridou et al., 2010; O'Keane et al., 2011; Yim et al., 2009). Hyper- and hypo-secretion of cortisol, and CRH deficiency have been linked to depression in non-pregnant and non-postpartum individuals as well (Charmandari et al., 2005; Chrousos, 1995; Tsigos and Chrousos, 2002).

In addition to their individual effects, the pro-inflammatory response and the HPA axis exhibit significant bidirectional interactions via the well-documented cytokine–glucocorticoid feedback circuit (Besedovsky and del Rey, 1996; Elenkov, 2008; Elenkov et al., 2005). In this circuit, an infectious or potentially injurious stressor increases production of pro-inflammatory cytokines, which in turn activate the HPA axis, increasing cortisol secretion.

Rising cortisol levels then bind to glucocorticoid receptors, including white blood cell glucocorticoid receptors (Pace and Miller, 2009), ultimately turning off further transcription of pro-inflammatory cytokines such as interleukin-10 (IL-10). The net effect of this feedback circuit is to alert the central nervous system to the risk of an infectious or injurious stressor, while at the same time limiting a potentially damaging or prolonged pro-inflammatory response and constraining further cortisol secretion. If this circuit is disrupted, the ability of cortisol to limit inflammation may be lost (Miller et al., 1999, 2002, 2008, 2009; Pace et al., 2012), leading to dysregulation of both cytokine production and cortisol secretion (Corwin et al., 2013). Nearly two decades ago, Chrousos and Tsigos suggested that disruption in the HPA axis-immune system bidirectional relationship could increase susceptibility to PPD (Chrousos, 1995; Tsigos and Chrousos, 2002). To our knowledge, this hypothesis has not yet been tested.

1.1. Research question

The inflammatory immune system and the HPA axis function in a complex, inter-dependent manner over time to maintain baseline and stress-related homeostasis. Abnormal inflammation or dysregulation of the HPA axis has the potential to disrupt the relationship, carrying adverse consequences for mental and physical health. In light of the significant inflammatory and HPA axis changes following labor and delivery, and the known associations between depression, inflammation, and abnormal HPA axis activity in other populations (Anisman and Merali, 2003; Raison et al., 2006), we tested the hypothesis that dysregulation in the bidirectional relationship between inflammation and the HPA axis early in the postpartum period would be associated with an increased risk of PPD in otherwise healthy women.

2. Materials & methods

2.1. Procedure

Procedures were described in detail in a previous report identifying a pattern of glucocorticoid resistance in the 3rd trimester of pregnancy in the minority and low-income women enrolled in this study (Corwin et al., 2013). Briefly, women who responded to ads placed in community and clinic sites were recruited in their 2nd or early 3rd trimester of pregnancy. Following a screening interview, those meeting inclusion criteria were visited at home by a registered nurse a total of 7 times for data collection; once between 32 and 36 weeks of pregnancy and again at weeks one and two, and months 1, 2, 3, and 6 after delivery. At the prenatal home visit, participants reviewed with the nurse the study protocol and provided informed consent for their participation. Participants next completed a demographic questionnaire providing information on age, marital status, race/ethnicity, personal and family history of depression, and whether or not they received government assistance through the Women, Infants, and Children (WIC) assistance program. Self-report of height, and pre-pregnancy weight was used for determination of pre-pregnancy body mass index (BMI). At this visit and at all subsequent home visits, women also completed questionnaires on current health status and on the presence of depressive symptoms via completion of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and perceived stress. Any subject scoring high ($\geqslant 10$) on the EPDS or answered positively on the self-harm question were interviewed by the nurse and the psychiatric provider for any needed referrals or immediate intervention.

After completing all self-report tools, blood was drawn from the antecubital vein into EDTA-containing tubes for later measurement