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Associations of postpartum sleep, stress, and depressive symptoms with LPS-stimulated cytokine production among African American and White women

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ABSTRACT

Background: Postpartum is a period of unique psychosocial stress characterized by sleep disturbance, risk for depressed mood, and heightened parenting stress. However, data on effects of these exposures on inflammatory immune function are limited.

Methods: This study examined associations among sleep, psychosocial stress (i.e., parenting stress, general perceived stress), mood (i.e., depressive symptoms), serum cytokine levels, and LPS-stimulated proinflammatory cytokine production among 69 women (32 African American, 37 White) assessed at 7–10 weeks postpartum.

Results: No associations between behavioral measures and serum cytokine levels were observed among women of either race. In African American women, but not Whites, poorer sleep quality, greater parenting stress, and greater depressive symptoms were associated with greater LPS-stimulated IL-6 and IL-8 production (ps ≤ 0.05). Also in African Americans, greater general perceived stress was associated with greater IL-8 production, and greater depressive symptoms with greater stimulated TNF-α production (ps ≤ 0.05). Simple mediation models highlighted the bidirectional relationship between stress and sleep in relation to inflammation among African American women.

Conclusions: Significant effects of both stress/distress and poor sleep quality on proinflammatory cytokine production during postpartum were observed uniquely among African American women. These data are consistent with an allostatic load model which predicts that conditions of chronic stress impart vulnerability to dysregulated responses to novel stressor exposures. The bidirectional nature of the stress-sleep relationship has clinical relevance. Studies examining whether interventions focused on one or both of these psychological factors during postpartum is beneficial for inflammatory profiles would be informative. In addition, examination of these models in relation to maternal health at postpartum, including delivery related wounds and other infections, is warranted.

1. Introduction

Postpartum is a period of unique psychosocial stress characterized by sleep disturbance and heightened stress. Reflecting partial sleep deprivation and fragmentation in response to the newborn's sleep-wake cycle, women spend an estimated 3 times longer awake after nocturnal sleep onset during the first several weeks postpartum compared to pregnancy or non-postpartum women with children. (Yamazaki et al., 2005; Doering, 2013; Montgomery-Downs et al., 2010; Nishihara and Horiuchi, 1998; Swain et al., 1997; Gay et al., 2004). Severity of postpartum sleep disruption is predictive of declines in marital satisfaction as well as risk for depression (Medina et al., 2009; Sleep, 2015; Bhati and Richards, 2015; Hiscock et al., 2006; Bayer et al., 2007; Hiscock et al., 2008; Dennis and Ross, 2005; Okun et al., 2011a). Moreover, stress specific to parenting is of particular relevance at postpartum; caring for a newborn entails changes in daily tasks, reductions in personal and partner time, and may introduce new financial challenges (Abidin, 1992; East and Barber, 2014; Chang et al., 2004). Further, a mother's experience of parenting as rewarding versus stressful is affected by her perceptions of both bonding with the child and the child's temperament (Abidin, 1992; East and Barber, 2014; Chang et al., 2004).

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In the context of these significant psychosocial stressors, women also experience unique physiological vulnerabilities. Infections are the most common cause of serious maternal morbidity at postpartum (Hebert et al., 1999). In the US, an estimated 32.2% of women undergo Cesarean-section, while 11.6% of those delivering vaginally have an episiotomy, which both necessitate wound healing (Friedman et al., 2015; Hamilton et al., 2015). Infections of delivery-related wounds, as well as uterine, bladder, and kidney infections and mastitis are common in postpartum, affecting 6.0–7.4% of women in the first month alone (Yokoe et al., 2001). As the majority of US deliveries occur in a hospital setting, exposure to hospital acquired-infectious illnesses including methicillin-resistant *Staphylococcus aureus* (MRSA) and group A streptococcus (GAS) can be of concern (Saiman et al., 2003; Chuang et al., 2002). Further, based on epidemiological data, the CDC now recognizes women in the first two weeks postpartum as a high risk group for acquiring seasonal influenza virus infection (Louie et al., 2009; Grohskopf et al., 2013). For these reasons, implications of sleep- and stress-induced immune dysregulation at postpartum have particular relevance.

The psychoneuroimmunology literature has delineated bi-directional associations between behavioral factors and immune function, with extensive research linking both impaired sleep and exposure to stressors with inflammatory dysregulation (Christian, 2012; Segerstrom and Miller, 2004a). Various studies link poorer self-reported sleep as well as experimentally-induced sleep restriction with increases in circulating inflammatory mediators and exaggerated ex vivo stimulated cytokine production (Van Leeuwen et al., 2009; Frey et al., 2007; Meier-Ewert et al., 2004; Prather et al., 2009; Okun et al., 2007a; Irwin et al., 2010). Moreover, data from the past three decades has established that both stressor exposure and depressive symptoms are associated with elevations in circulating inflammatory markers, as well as enhanced stimulated cytokine production (Haapakoski et al., 2015; Steptoe et al., 2007; Dowlati et al., 2010; Rohleder, 2014). Although similar effects have been observed in perinatal women, data specific to this population is sparse and has focused primarily on pregnancy rather than postpartum. For example, sleep disturbance in pregnant women has been associated with elevations in serum proinflammatory cytokines, including IL-6 and IL-8 (Okun et al., 2007b, 2011b; Blair et al., 2015). Moreover, among pregnant women, greater stress or depressive symptoms have been associated with elevations in serum cytokines, exaggerated ex vivo stimulated cytokine production, and exaggerated inflammatory responses to the seasonal flu vaccine (Coussons-Read et al., 2007; Christian et al., 2013a, 2009a).

As described by the allostatic load model, while neuroendocrine and immune responses are adaptive in the face of stressful situations, repeated or prolonged activation of the stress response can impair the body's ability to maintain allostasis (McEwen, 1998). This model predicts that conditions of chronic stress impart vulnerability to dysregulated responses to novel or additional stressor exposures (Juster et al., 2010). Thus, allostatic load is a pathway by which chronic stress associated with racial minority status may confer risk for poor health outcomes (Williams, 1999; Chen et al., 2014). Consistent with this notion, prior data, including that from our group, suggest that African American women may be particularly vulnerable to stress-induced immune dysregulation. For example, our data show that during pregnancy and non-pregnancy, African-American women exhibit more exaggerated increases in serum interleukin(IL)-6 upon exposure to an laboratory acute stressor (Trier Social Stress Test) as compared to White women (Christian et al., 2013b). Moreover, our data have shown that, compared to Whites, African American women show greater increases in serum IL-8 and related increases in risk for preterm birth in the context of poor sleep as measured at mid-gestation (Blair et al., 2015). However, racial differences in associations between psychosocial factors and inflammation at postpartum remain relatively unexamined.

The current study examined associations among sleep, psychosocial stress (i.e., parenting stress, general perceived stress), mood (i.e., depressive symptoms), serum cytokine levels, and LPS-stimulated proinflammatory cytokine production among 69 women (32 African American, 37 White) assessed at 7–10 weeks postpartum. It was hypothesized that women reporting poorer sleep, greater stress (e.g., general perceived stress, parenting stress), and/or depressive symptoms would exhibit elevated serum proinflammatory cytokine levels and exaggerated cytokine production. It was also hypothesized that these effects would be exacerbated among African Americans versus Whites. Potential mediating pathways linking sleep, stress/distress, and inflammation were examined.

2. Methods

2.1. Study design and participants

This study enrolled 84 women from The Ohio State University Wexner Medical Center (OSUWMC) and surrounding community of Columbus, Ohio. Exclusion criteria consisted of multi-fetal gestation, diagnosed fetal anomaly, health conditions or use of medications with a clear immunological or endocrinological component (e.g., cancer), illicit drug use other than marijuana, and consumption of > 2 alcoholic beverages per week per self-report or medical record at time of enrollment. Women reporting acute illness, such as cold- or flu-like symptoms, or antibiotic use within ten days of a study visit were rescheduled.

The full study included three prenatal assessments. However, the current analyses focused only on data from the 7–10 week postpartum visit. At the study visit, women provided a blood sample and completed psychosocial questionnaires. Women were excluded from the current analyses if they did not attend the postpartum visit (n = 11), were missing cytokine data (n = 2), or experienced fetal death or infant mortality (n = 2), resulting in a final analytic sample of 69. The study was approved by The Ohio State University Biomedical Institutional Review Board. Written informed consent was obtained from all participants and modest compensation provided.

2.2. Demographic characteristics

Race, marital status, age, education, annual household income, parity (primiparous/multiparous), and breastfeeding status (yes/no) were determined by self-report. Maternal body mass index (BMI; kg/m^2) was calculated using weight and height measured by nursing staff at the study visit.

2.3. Psychosocial and behavioral measures

The Pittsburgh Sleep Quality Index (PSQI) was used to assess overall sleep quality (Buysse et al., 1989). A score > 5 is indicative of clinically disturbed sleep. This measure includes seven subscales: subjective sleep quality, sleep latency (i.e., time to fall asleep), sleep duration, habitual sleep efficiency (i.e., time asleep/time in bed*100), sleep disturbance, use of sleeping medications, and daytime dysfunction. In the current study, all subscales were reported as sum scores using their original scale (e.g., minutes). The total PSQI score was calculated per guidelines (Buysse et al., 1989). The PSQI has high diagnostic sensitivity and specificity in distinguishing good and poor sleepers (Buysse et al., 1989).

The Parenting Stress Index – Short Form (PSI-SF) is a widely used 36-item measure of stress as a result of the parent-child relationship. (Abidin, 1990; Haskett et al., 2006) Three subscales comprise the PSI: parental distress, parent-child dysfunctional interaction, and difficult