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Racial discrimination and leukocyte glucocorticoid sensitivity: Implications for birth timing

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ABSTRACT

Rationale: Psychological stress-induced cortisol elevations appear to contribute to preterm birth. Yet, some studies suggest that the biological ramifications of racial discrimination-associated stress are unique and may involve development of decreased glucocorticoid sensitivity despite normalized cortisol levels.
Objective: In this study, we examined the effects of racial discrimination on maternal cortisol output, leukocyte glucocorticoid sensitivity, and the degree of correspondence between cortisol levels and birth timing in an African American cohort.
Method: A generally healthy prospective cohort was enrolled at 28–32 weeks gestation ($n = 91$). The Experiences of Discrimination scale was administered, whole blood collected, and plasma cortisol levels, cytokine levels, and leukocyte counts quantified for examination of patterns of endogenous feedback.
Results: Racial discrimination in the mid-tertile was associated with greater maternal cortisol levels than the bottom tertile among women reporting internalizing responses ($b^* = 0.68$, $p = 0.001$). Decreased leukocyte glucocorticoid sensitivity was witnessed at greater frequencies of experiences of racial discrimination, as evidenced by decreased correspondence between maternal cortisol levels and plasma IL-8 levels, monocyte counts, and lymphocyte counts (p values ≤ 0.043). The association between maternal cortisol levels and birth timing differed by discrimination tertile (p *values* ≤ 0.005), with greater cortisol levels predictive of earlier birth among women without ($b^* = -0.59$, $p < 0.001$) but not with racial discrimination ($ps \geq 0.497$).
Conclusion: We provide novel evidence of decreased glucocorticoid sensitivity at increasing frequency of exposure to racial discrimination. Our findings suggest that the biology of preterm birth may depend upon racial discriminatory exposures, favoring pathways dependent upon glucocorticoid-induced increases in leukocyte tissue surveillance versus glucocorticoid resistance-associated inflammatory aberrations at increasing levels of exposure. Precision approaches to prenatal care are sorely needed to combat preterm birth, particularly among African American women, with efforts dependent upon further research examining the pathways contributing to the syndrome dependent upon the totality of an individual's exposures.

1. Introduction

African American women exhibit the highest U.S. rates of preterm birth, which contributes to a two-fold increased risk for mortality among African American versus European American infants (Martin et al., 2017; Matthews et al., 2015). There is strong evidence to suggest that a disproportionate burden of traditional risk factors (e.g., socioeconomic inequities; Colen et al., 2018) do not fully account for racial disparities witnessed in health, with discriminatory exposures related to racial minority status implicated as an important contributing factor. In fact, both perceived and objectively quantified exposure to racial discrimination have been linked to increased odds of preterm birth in African American samples (Chae et al., 2018; Rankin et al., 2011; Ruiz et al., 2014). Consistent with the conceptualization of racial discrimination as a psychological stressor (Berger and Sarnyai, 2015), a large literature also links alternative forms of psychological stress to preterm birth (Manuck et al., 2015; Staneva et al., 2015).

More recent work has aimed to identify mechanisms by which psychological stress affects birth timing, with several studies now showing that greater maternal output of the glucocorticoid cortisol mediates associations between several forms of stress and earlier birth (Gillespie et al., 2017; Hoffman et al., 2016; Mancuso et al., 2004). Yet, emerging evidence also suggests that the biological ramifications of discrimination are unique, with greater perceptions of lifetime racial discrimination associated with perturbations in diurnal patterns of cortisol but not with elevations in average output by adulthood (Adam

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et al., 2015). Such findings are consistent with studies assessing cortisol levels among pregnant African American versus European American women (Christian et al., 2016; Simon et al., 2016) and may explain why no study has linked racial discrimination to birth timing via elevations in maternal cortisol output. We are also unaware of any studies publishing null findings.

Of relevance, some forms of psychological stress, particularly those social in nature, have been shown to induce decreased glucocorticoid sensitivity that persists despite normalization of total glucocorticoid output (Jarcho et al., 2013; G. E. Miller, Cohen and Ritchey, 2002; G. E. Miller, Gaudin, Zysk and Chen, 2009; Powell et al., 2009; Walsh et al., 2018). Glucocorticoid sensitivity among stressed groups has been evaluated using several well-developed methods, including by identifying deviations from expected associations among *in vivo* glucocorticoid levels, cytokine levels, and patterns of leukocyte trafficking (e.g., Cohen et al., 2012; Cole, 2008; Cole et al., 2009).

To our knowledge, leukocyte glucocorticoid sensitivity has been the topic of only one study of pregnant women, with results providing support for an association between minority status and decreased sensitivity to cortisol's anti-inflammatory effects (Corwin et al., 2013). Whether racial discrimination is associated with decreased leukocyte glucocorticoid sensitivity remains to be determined, though the progressive development of this aberration may help to explain the exaggerated, prolonged inflammatory response to social threat witnessed among African Americans reporting more discriminatory exposures (Lucas et al., 2017). This holds important implications for the study of racial disparities in disease processes with inflammatory underpinnings, such as preterm birth (reviewed by Romero et al., 2014).

In this study, we examined the effects of racial discrimination on maternal cortisol output and leukocyte glucocorticoid sensitivity among pregnant African American women. We hypothesized that while discrimination would not be associated with cortisol output, women with racial discriminatory exposures would show evidence of decreased leukocyte glucocorticoid sensitivity. We also tested the hypothesis that maternal cortisol levels would show diminished correspondence with birth timing among women with increasing frequencies of experiences of racial discrimination, which may be attributable to the presence of decreased glucocorticoid sensitivity.

2. Method

2.1. Study design and participants

This prospective cohort study recruited a convenience sample of pregnant women attending two large Midwestern prenatal clinics. Pregnant community members were also recruited by advertisement. Enrollment occurred from September 2013 to June 2015, with participants attending a single study visit at 28 weeks 0 days' to 32 weeks 6 days' gestation and followed prospectively to birth to allow for medical record review and clinical data abstraction.

Eligible women were aged 18 to 34 and self-reported African American race, non-Hispanic ethnicity, and birth in the United States. Women reporting tobacco or marijuana use beyond the first trimester or other illicit drug use at any point in pregnancy were not eligible. Women reporting height and pre-pregnancy weight consistent with underweight (body mass index < 18.5) or obese class III (body mass index ≥ 40) classifications were not eligible (World Health Organization, 2000). To enhance accuracy of gestational age estimates, ultrasound dating at ≤ 15 weeks of pregnancy was required for participation (American College of Obstetricians and Gynecologists, 2014). To reduce the potential influence of confounding factors and promote the opportunity to observe women undergoing spontaneously-initiated birth, those with chronic endocrine- or immune-impacting conditions (e.g., sickle cell disease, inflammatory bowel disease), regularly taking endocrine- or immune-impacting medications (e.g., corticosteroids), diagnosed with a major complication of pregnancy (e.g., fetal anomaly, gestational diabetes, gestational hypertensive disorders), or receiving interventions to prolong pregnancy (e.g., cervical cerclage, progesterone) were ineligible. Yet, several women were diagnosed with complications of pregnancy following enrollment.

All participants completed informed consent and received modest payment in the form of a gift card at the time of enrollment. The study was approved following review by The Ohio State University Biomedical Institutional Review Board and the OhioHealth Institutional Review Board.

2.2. Sample demographic, health, and psychosocial characteristics

The demographics and health behaviors of participants were assessed by self-report. Height measured at the study visit and self-reported pre-pregnancy weight were used to calculate pre-pregnancy body mass index (BMI; kg/m^2) according to the definition set forth by the World Health Organization (2000). Non-smoking was defined as no smoking during pregnancy, including during early pregnancy, as all participants were required to report quitting by the second trimester to be eligible for participation. Sleep quality was also assessed using the Pittsburgh Sleep Quality Index (PSQI), which produces a global sleep quality score ranging from 0 to 21 with higher scores indicative of worse sleep quality. The PSQI has a Cronbach's α of 0.83 at the individual item level and test-retest reliability of 0.85 for global scores (Buysse et al., 1989). During pregnancy, sleep quality assessed by the PSQI appears to be susceptible to both the physiologic changes associated with the growing fetus (Sedov et al., 2018) and psychological factors (Francis et al., 2017). The 14-item Perceived Stress Scale (PSS) was administered to quantify perceptions of stress within the month prior to the study visit (Cohen et al., 1995). With a range of 0–56, higher scores on the PSS are indicative of greater perceived stress. The psychometrics of the scale have been extensively tested across various populations, including during pregnancy (Bann et al., 2017).

2.3. Racial discrimination

The Experiences of Discrimination Scale (EOD) was administered to assess lifetime exposure to discrimination on the basis of race, ethnicity, or color. Participants are asked how many times (0, 1, 2, or 3+) they have experienced discrimination in each of nine life situations (e.g., at school, at work, getting medical care), producing a score with a range of zero to 27. Among African American samples, Cronbach's α reaches 0.86 and test-retest reliability 0.70 (Krieger et al., 2005), which is consistent with a Cronbach's α of 0.82 witnessed for the current study. Due to the extreme positive distribution of EOD frequency scores, a tertile split was applied to produce groups reflective of EOD frequency = 0 (Tertile 1), EOD frequency = 1–2 (Tertile 2), or EOD frequency ≥ 3 (Tertile 3).

2.4. Biological parameters

Antecubital or distal venipuncture was performed between 1100 and 1600 h at a single time point to obtain heparinized and K_2EDTA-preserved whole blood. For participants reporting recent cold- or flu-like illness during visit confirmations, study visits were rescheduled at least one week removed from resolution of symptoms. Participants were asked to refrain from exercise or caffeine use on the day of the visit and to wake at least 2.5 h prior to the study visit (Bessinger et al., 2002; R. Miller et al., 2016; Tsubouchi et al., 2006).

As reported previously in detail (Gillespie et al., 2017), in batches, total plasma cortisol levels (ng/ml) were assayed in duplicate by solid phase competitive enzyme-linked immunosorbent assay (Calbiotech, Spring Valley, CA) and spectrophotometry (BioTek PowerWave Microplate Spectrophotometer, Winooski, VT), producing intra- and inter-assay coefficients of variation of 3.7% and 9.7%, respectively.

Plasma cytokine levels (pg/ml) were quantified in duplicate using