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African American Women Experience Over One and a Half Times the Rate of PTB

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Introduction

African American women in the United States (US) experience over one and a half times the rate of PTB (14.1% vs. 9.1%) and nearly double the risk of early PTB (<32 weeks) compared to US white women [1]. Their infants are twice as likely to die [2]. More than a decade ago, the National Academy of Medicine identified chronic stress experienced by African American women as one of the key factors contributing to this elevated risk. Unfortunately, in the decade since, there has been little if any improvement in birth outcomes among the population, and this health disparity has continued unabated. Therefore, in order to better address this intractable problem, our team of experts with complementary skills in prenatal health, stress research, health disparity, and metabolomics came together with a fresh approach. As a group, and as described in our recent article, "Metabolites and Metabolic Pathways Associated with Glucocorticoid Resistance in Pregnant African-American Women", [3] we identified for the first time, the metabolites and metabolic pathways that associated with increased chronic stress within a socioeconomically diverse cohort of pregnant African American women, an essential first step in the successful development of a targeted intervention. For our study, the level of chronic stress exposure was determined by the concentration of the cortisol-like steroid dexamethasone (Dex) required to produce a 50% inhibition (i.e., Dex IC50) of the *invitro* release of the cytokine tumor-necrosis-factor alpha (TNF-alpha) from white blood cells in response to a standard dose of lipopolysaccharide (LPS); this variable, Dex IC50, is commonly defined as glucocorticoid resistance.

Discussion

To identify the metabolites and metabolic pathways associated with glucocorticoid resistance, we conducted untargeted High-Resolution Metabolomics (HRM) profiling on venous blood samples collected from 273 pregnant African American women ages 18-40, who were between 8-14 weeks pregnant. Participants were not taking any chronic medications except prenatal vitamins and had no chronic health conditions. Using Metabolome-Wide Association Studies (MWAS) and pathway enrichment analysis, we then identified the key metabolites altered in association with chronic stress as being those associated with energy production (nicotinamide and TCA cycle), amino acid availability, and glycosphingolipid metabolism. The associated metabolic pathways in turn were all clearly physiologically relevant for a healthy pregnancy and/or fetal development and included pathways associated with inflammation, oxidative stress, and growth and development. This study also identified a wide range of glucocorticoid resistance (reflecting chronic stress exposure) across the cohort, indicating somewhat surprisingly that the level of exposure to chronic stress in this population was not associated with age or parity or with standard indicators of socioeconomic status (SES) including education or insurance status. This supports the consensus that African American women are uniquely subject to high levels of intersectional stress related to chronic discrimination due to their race, sex, and class (often reflective of neighborhood) [4]. AA women also are uniquely identified as subject to the intergenerational transmission of stress received from their own mothers [5] as well as transmitting that stress to their offspring. The concept of chronic stress exposure across the lifetime in African American women was identified nearly thirty years ago by Geronimus as "weathering" [6]; a term that continues to be used today as a framework for better understanding the biological impact chronic stress exerts on African American women, including on pregnancy outcomes [6-8]. Interesting and pertinent to the findings of our current study, is that recent research also identifies that among African America women, greater SES is actually associated with increased reports of both racial discrimination and symptoms of depression, not lower [9]. Evidence indicating shortened telomeres in non-pregnant African American women compared to age-matched White women [10] likewise suggests that this population experiences a biological vulnerability that underlies a number of adverse health outcomes-including adverse birth outcomes-disproportionately experienced by African American women.

Conclusion

In the current study, we added to this important body of literature, by identifying several critical metabolites and metabolic pathways differentially expressed based on chronic stress exposure in pregnant African American women independent of typical socioeconomic indicators. Clinical implications of our findings might include identifying ways to assist pregnant women to minimize their exposure to stressors, or perhaps more realistically, interventions aimed at providing women alternative ways to respond to those stressors, for example by taking walks, or through cognitive behavioral therapy or mindfulness practice. Likewise, clinical interventions

focused on heightened monitoring for early indications of pregnancy complications within this population of women at high risk of intersectional stressors could be implemented as standard of care. Ideally, societal level changes to reduce racism, and improve access to quality health care would also be of benefit, with metabolomic analyses potentially providing an objective measure of their success.

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