Racial/Ethnic Differences in Self-Reported and Biologic Measures of Chronic Stress in Pregnancy

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Abstract

Objective—Racial differences in chronic maternal stress may contribute to disparities in pregnancy outcomes. The objective is to identify racial and ethnic differences in self-reported and biologic measures of stress between non-Hispanic black (NHB) and non-Hispanic white (NHW) pregnant women.

Study Design—NHB and NHW pregnant women were enrolled prior to 23 weeks gestation in this prospective cohort study. Equal numbers of women were recruited with public versus private insurance in each racial group. Self-reported stress was measured and blood samples collected in the 2nd and 3rd trimesters were analyzed for serum Epstein - Barr virus (EBV) antibody, C-reactive protein (CRP), corticotropin-releasing hormone (CRH), and adrenocorticotropic hormone (ACTH).

Results—112 women were enrolled. NHW women reported more buffers against stress (p=0.04) and neighborhood satisfaction (p=0.02). NHB women reported more discrimination (p<0.001), food insecurity (p=0.04) and had significantly higher mean CRP levels and mean ACTH levels in the 2nd and 3rd trimesters.
Conclusion—Significant differences in self-reported and biologic measures of chronic stress were identified between NHB and NHW pregnant women with similar economic characteristics. Future studies should investigate mechanisms underlying these differences and their relationship to pregnancy outcomes.

INTRODUCTION

Preterm birth is the major cause of perinatal morbidity in the United States, accounting for 85% of adverse perinatal outcomes.1 Infants born prematurely (<37 weeks gestation) have an increased risk of neonatal mortality as well as serious health problems such as respiratory disease, blindness and cerebral palsy. In 2005, the annual societal economic cost associated with preterm birth in the United States was greater than $26.2 billion.2 The burden of preterm birth and its associated adverse outcomes is not equally distributed by race/ethnicity. Large disparities in preterm birth rates exist with non-Hispanic blacks having nearly double the risk of preterm birth when compared to non-Hispanic whites.2 In addition, preterm birth accounts for 80% of the black/white infant mortality gap.3

Unfortunately, because the etiology of spontaneous preterm birth remains unclear, both an understanding of the basis for disparities in birth outcomes and effective prevention strategies remain limited. While socioeconomic status and psychosocial stress both have been associated with preterm birth, the specific biologic mechanisms linking these factors to preterm birth and its disparities remain unclear.4-12

There are three physiologic pathways that support a link between maternal stress and preterm birth.13 First, stress activates the hypothalamic-pituitary-adrenal (HPA) axis stress response, resulting in increased corticotrophin-releasing hormone (CRH), and an increase in placental CRH. The increase in CRH leads to increased cytokine release from the decidua and amnion which can stimulate myometrial contractions,14-16 potentially linked to the onset of preterm labor.17-19 Second, chronic stress is linked to increased glucocorticoid production, and inhibition of immune function.20 This stress-related suppression of immune functioning may lead to increased susceptibility to infection and preterm birth.13 Elevated Epstein-Barr Virus (EBV) titers, thought to be secondary to suppression of cell mediated immune functioning, have been shown to be associated with chronic stress.21, 22 Third, it has been reported that chronic stress may up-regulate the inflammatory response to trivial stimuli leading to a chronic pro-inflammatory state. Trivial inflammatory stimuli may then result in excessive cytokine production, stimulating myometrial contractions and preterm birth.23 Elevated C-Reactive Protein (CRP), a marker of inflammatory response, has been shown to be associated with chronic stress and has been reported in association with preterm birth.24-26

Although greater psychosocial stress among black women has been shown to be associated with preterm birth, few studies have demonstrated either increased psychosocial stress during pregnancy in black women or a racial disparity in psychosocial stress that is associated with a disparity in biologic measures.5 In addition, many studies comparing racial differences do not adequately account for differences in economic status between groups,
further limiting the ability to ascertain the independent association between stress, biologic measures, and preterm birth.

We hypothesize that racial differences in chronic maternal stress can be identified and may contribute to the persistent racial/ethnic disparities in rates of preterm birth. Chronic maternal stress can be assessed by measuring both self-reported stress as well as biologic markers of the stress response. Multiple measures of self-reported stress exist; however, a previously reported model of maternal stress including four key domains (external stress, buffers of stress, enhancers of stress, and perceived stress) provides a comprehensive approach to stress measurement. Biologic measures of stress were chosen for this study based on the proposed physiologic pathways linking stress and preterm birth, including measures of HPA axis (CRH / ACTH), inflammation (CRP) and a measure of innate immune function (EBV). The objective of this study is to identify racial and ethnic differences in self-reported and biologic measures of chronic stress between non-Hispanic black (NHB) and non-Hispanic white (NHW) pregnant women with similar economic characteristics.

**MAtErials and Methods**

For this prospective cohort pilot study, the Stress in Pregnancy Study (SIPS), pregnant women were recruited between May 2008 and July 2009 from two prenatal clinics associated with an urban, university hospital in Chicago, Illinois. Since it was impossible to know a women’s income level prior to enrollment in the study, coverage by Medicaid (public health insurance) was used as a proxy measure for a low income level of potential participants. Consecutive women in the prenatal clinic were approached, with the intent to enroll a final sample size of 100 women made up of 50 NHB and 50 NHW women with each racial group recruited specifically to have half Medicaid and half private insurance. This was accomplished by recruiting from a prenatal clinic serving predominantly Medicaid patients and a second prenatal clinic serving the same urban hospital that required private insurance. All women were screened for eligibility criteria prior to enrollment. More than 100 women were ultimately consented to account for loss to follow up.

English-speaking pregnant women who were at least 18 years old and less than 23 weeks gestation at enrollment were eligible to participate. Women were excluded if they had a multi-fetal gestation, prior cervical surgery, prolapsed amniotic membranes, current or planned cervical cerclage, progesterone treatment after 14 weeks during the current pregnancy, prior preterm birth, congenital Mullerian abnormality, or other maternal chronic condition known to increase the risk of preterm birth (hypertension, systemic lupus erythematosus, pre-pregnancy diabetes mellitus, HIV).

Self-reported stress was measured using validated scales representing four domains of maternal stress (external stress, buffers of stress, enhancers of stress, and perceived stress) during interviews conducted in prenatal clinics between 14 and 22 weeks of gestation. Stress scales were chosen based on the above published model of stress, a review of the literature published by our team on self-reported stress scales utilized in preterm birth research, and expert consensus. External stressors were measured using the Home Hardships Scale,
the USDA Household Food Security Scale, and the Neighborhood Satisfaction Scale.\textsuperscript{29-31} Buffers of stress were measured using the State Hope Scale, the Medical Outcomes Study-Social Support Survey (MOS-SSS), and the “Buffers of Stress Index.”\textsuperscript{32,33} Enhancers of stress were measured using the Center for Epidemiologic Studies-depression Scale (CES-D).\textsuperscript{34} Several scales were used to measure perceived stress, including the Perceived Stress Scale,\textsuperscript{35} the Prenatal Distress Questionnaire,\textsuperscript{36} and the Krieger Perceived Racism Scale.\textsuperscript{37} Biologic measures of stress, including measures of HPA axis (CRH/ACTH), inflammation (CRP) and a measure of innate immune function (EBV), were selected based on literature review and expert consensus. Two blood samples were collected by phlebotomists during the participants’ regularly scheduled prenatal visit. The first sample was obtained in the second trimester between 14 and 23 weeks and the second sample was obtained in the third trimester between 28 and 33 weeks of gestation. Blood samples were immediately processed. CRP and EBV samples were centrifuged for 20 minutes at 2,000 RPM, aliquoted into 2 cryovials, and then stored at -70°C until analysis. ACTH and CRH samples were allowed to clot for 30 minutes at room temperature and then centrifuged for 20 minutes at 2,000 RPM. ACTH and CRH samples were aliquoted into cryo-vials and stored at -70°C until analysis. EBV, CRP, CRH, and ACTH were analyzed using highly sensitive, standardized enzyme immunoassay protocols. The quantity of CRP in each sample was determined based on comparison with calibrators standardized against International Reference Preparation CRM 470 (Dade Behring #0QKZ, Deerfield, IL, United States). Antibodies against EBV were quantified using a commercially available enzyme immunoassay kit for measuring EBV viral capsid antigen immunoglobulin G (IgG) antibodies in serum (DiaSorin #P001606A, Stillwater, MN, United States). ELISA was performed for the quantification of ACTH and CRH in the plasma samples. Both kits (#21-ACTHU-E01 and #20-CRFHU-E01) were acquired from Alpco Diagnostics (Salem, NH, United States) and were performed according the manufacturers instruction.

All continuous data were evaluated for normal distribution using the Kolmogorov-Smirnov test. If non-normal distribution was detected, the data were subjected to log transformation and re-analyzed for normality. Analysis of biomarker data was performed on log-transformed data with non-transformed means ± SD reported. The data were evaluated using the student t-test for continuous variables and chi-square for categorical variables. All tests were two-tailed and alpha = 0.05 was used to determine significance. Data analysis was performed using SPSS for Windows, version 19 (SPSS Inc, Chicago, IL).

Results

Of the one hundred and twelve pregnant women enrolled, 57 were NHW (28 Medicaid and 29 private insurance) and 55 were NHB (26 Medicaid and 29 private insurance). Demographic characteristics of the 112 women are shown in Table 1. Health insurance status (private versus public insurance) was not significantly different between the two racial groups. Public health insurance (Medicaid) was highly correlated with reported household income less than $30,000. Women reporting total household income between $30,000 and $100,000 were evenly split between public versus private insurance, and all women reporting income greater than $100,000 had private insurance. Fifteen of the 112 women
declined to report their household income level; of the women refusing to report their income level, 8 were NHB and 7 were NHW. Among women reporting their household income level, there was no significant difference by race/ethnicity. Nevertheless, demographic differences still existed between the two groups. NHB women were significantly more likely to be single, have a BMI greater than 30, and have a lower level of education.

NHW women reported higher buffers against stress as measured by the Buffers of Stress Index (p=.04) and increased neighborhood satisfaction (p=0.02). NHB women reported higher rates of discrimination (p<.001), depression (p=0.05), and food insecurity (p=0.04) (Table 2). NHB women had significantly higher mean CRP levels in the 2nd trimester (12.7 ± 11.9 vs. 7.4 ± 8.3, p < .01) and 3rd trimester (12.2 ± 14.9 vs. 6.9 ± 7.4, p = .04) relative to NHW women. NHB women also had significantly higher ACTH levels in the 2nd trimester (21.6 ± 11.9 vs. 16.5 ± 8.5, p = .01) and 3rd trimester (6.4 ± 15.1 vs. 3.9 ± 4.0, p = .03) relative to NHW women. No differences in EBV or CRH levels were detected between the two racial/ethnic groups (Table 3).

**Comment**

This study of NHB and NHW pregnant women reveals significant differences in self-reported and biologic measures of chronic stress regardless of income and health insurance coverage. Even after accounting for income status, differences in chronic stress between the two groups persisted. Specifically, NHB women reported greater perceived discrimination and external stressors and fewer buffers against stress. NHB women also were found to have higher levels of biologic markers of stress, CRP and ACTH, in both the 2nd and 3rd trimesters of pregnancy.

Racial differences in chronic stress have been proposed as a possible driver of persistent racial disparities in preterm birth rates. Given that preterm birth rates have been reported to be higher for NHB women compared to NHW women regardless of economic status, it is important to understand how chronic stress differs by race/ethnicity after controlling for low-income. In this study, our aim was to have a similar number of NHB and NHW low income women participate by enrolling approximately equal numbers of women in each racial group with private and public health insurance.

Data support the hypothesis that chronic stress is not only associated with preterm birth, but also is a contributor to the racial disparities evident in preterm birth rates in the United States. Collins et al. performed a case-control investigation of African-American women with very low birth weight infants (VLBW). African-American mothers who perceived that their own stress was greater and that their neighborhood conditions were worse were found to have significantly increased odds of having a VLBW child. Additionally, it was noted that African-American women reporting higher lifetime exposure to interpersonal racism had significantly increased odds for VLBW infants even when controlling for demographic, biomedical, and behavioral variables.

In this study, similar numbers of NHB and NHW women were low income; however, significant differences in biologic measures of chronic stress were still identified. NHB
pregnant women were found to have higher levels of CRP and ACTH in the 2nd and 3rd trimesters. Outside of pregnancy, higher mean CRP levels have been reported in NHB women. Similar results were found in a cross-sectional analysis of a cohort of 775 pregnant women which showed that higher median CRP values were associated with black women. However, one recent study reported that a higher level of CRP among African-American women was associated with lower risk of anxiety. There are limited data on racial differences in CRP when the racial groups are stratified by low-income or public health insurance.

In addition, this study reveals higher levels of CRP in both the 2nd and 3rd trimesters among low income NHB women representing possible differences in inflammatory profiles during pregnancy. These differences may represent differences in underlying external stressors across groups. Other factors such as obesity and chronic disease have also been shown to be linked to differences in inflammatory response. High concentrations of CRP found in the earlier stages of pregnancy are positively associated with preterm delivery and an increased risk of fetal growth restriction and neonatal complications including preterm birth, low birthweight, and small size for gestational age. Higher CRP levels in NHB women in both the 2nd and 3rd trimesters may represent an important physiologic link between maternal stress, maternal inflammatory state, and adverse birth outcomes.

The study shows a significant difference in mean ACTH levels between NHB and NHW women in both the 2nd and 3rd trimesters, representing differences in ACTH response across pregnancy. Differences in ACTH between NHB and NHW women have not previously been reported.

A study measuring cortisol, ACTH, and CRH levels in 310 African American, Hispanic, and White women at three time points during pregnancy showed that (1) African-American women had lower levels of cortisol than non-Hispanic White women and (2) African-American women had higher levels of ACTH than Hispanic women. Differences by ethnicity in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (cortisol, ACTH) have also been reported, but these differences have not been definitively linked to maternal stress. It is still unknown whether these differences play a role in explaining the racial disparities in birth outcomes.

The results show not only racial differences in biologic measures of stress across pregnancy, but also differences in self-reported stressors such as discrimination, depression, and level of food insecurity. Prior studies have shown that high levels of self-reported experiences of racial discrimination are associated with both preterm and low birth weight deliveries and may be a mechanism for differences in life course stress across racial groups, regardless of income levels. These findings add to the biologic plausibility that racial disparities in birth outcomes may be related to social determinants of health and the corresponding alterations in biologic measures that they engender.

This study also finds that NHB women reported higher levels of depression and food insecurity. It has been reported that higher levels of perceived racial discrimination may increase symptoms of depression. NHB women reported higher rates of food insecurity.
despite a similar proportion of low income women in each racial group. Higher food insecurity may be an indication that NHB pregnant women experience poverty with fewer safety nets than low-income NHW pregnant women and may be experiencing a higher rate of household stressors related to poverty. In a study of 606 low and middle-income pregnant women, black race was also reported to be a predictor for household food insecurity.\textsuperscript{56}

In our study, NHW pregnant women reported significantly higher neighborhood satisfaction and higher buffers of stress such as coping mechanisms and social support as compared to NHB women. Several studies have reported that neighborhood characteristics, such as economic disadvantages, high rates of crime, and racial/ethnic segregation may be associated with adverse pregnancy outcomes.\textsuperscript{57,58} In addition, exposure to adverse neighborhood environments, especially violent crime, has been correlated with an increased prevalence of preterm birth.\textsuperscript{58,59} A study that focused on African-American women at a medical center in Chicago found that women who reported higher levels of perceived crime also reported higher levels of psychological distress, a key predictor of preterm birth.\textsuperscript{58}

NHW pregnant women in this study also reported higher overall buffers of stress based on the IRT optimized Buffers of Stress Index. Buffers of stress including improved self-esteem, coping, and other stress-resistance resources like optimism and social support help to facilitate adaptation during times of stress.\textsuperscript{57} Limited data have previously been reported on differences in buffers of stress across racial groups when controlling for economic status. Previous work by our group in a predominantly low-income African American population found that poor buffers of stress, such as coping skills, were associated with low birth weight infants (<2500g) and higher buffers of stress had a protective effect.\textsuperscript{60} Some studies have implied that self-esteem and personal mastery may be associated with birth outcomes, while others have concluded that there is no evidence to prove these resources buffer the effects of stress or prevent low birth weight or preterm birth.\textsuperscript{61,62}

Study limitations include the modest sample size. Additional racial and demographic differences might be detected with a larger sample and allow for regression analysis to further adjust for these differences. Additional social and environmental factors are likely to contribute to racial differences in maternal stress, but were not able to be adequately measured. Maternal insurance status and income level do not fully capture socio-economic status as reflected by differences in the marital status and education level between the two groups, although insurance status did serve as a useful proxy measure of SES to aid in recruiting racial groups with similar numbers of low-income women. Obesity and other physiologic differences between groups can contribute to differences in inflammation; a larger sample size would provide opportunity to control for these differences. The strengths of this study include its prospective nature, an enrollment design stratified by racial and income differences, and the combined measure of both self-reported and biologic measures of stress.

In summary, elevated chronic stress in NHB women may play a role in racial disparities in preterm birth. Significant differences in self-reported and biologic measures of chronic stress were identified between NBH and NHW pregnant women with similar economic
status. Future studies with larger sample sizes should further investigate the racial differences in chronic stress, associations with adverse pregnancy outcomes, and the physiologic mechanisms behind these disparities. With additional data to identify differences in social and environmental stressors in pregnancy across race/ethnicity, we can gain a better understanding of the biologic mechanisms for disparities in preterm birth. This will facilitate the use of targeted interventions to reduce these disparities and their associated adverse birth outcomes.

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|                        | Non-Hispanic Black N = 55 | Non-Hispanic White N = 57 | P      |
|------------------------|---------------------------|---------------------------|--------|
| **Marital Status**     |                           |                           |        |
| Single                 | 38 (69%)                  | 21 (37%)                  | <0.01  |
| Married                | 17 (31%)                  | 36 (63%)                  |        |
| **Health Insurance Status** |                       |                           |        |
| Private                | 29 (53%)                  | 29 (51%)                  | 0.84   |
| Medicaid               | 26 (47%)                  | 28 (49%)                  |        |
| **BMI**                |                           |                           |        |
| <30                    | 25 (45%)                  | 50 (88%)                  | <0.01  |
| >30                    | 30 (55%)                  | 7 (12%)                   |        |
| **Employed**           |                           |                           |        |
| Yes                    | 38 (69%)                  | 40 (70%)                  | 0.90   |
| No                     | 17 (31%)                  | 17 (30%)                  |        |
| **Education**          |                           |                           |        |
| ≤High school           | 7 (13%)                   | 3 (5%)                    | <0.01  |
| Some college           | 23 (42%)                  | 12 (21%)                  |        |
| ≥College               | 25 (45%)                  | 42 (74%)                  |        |
| **Income Level**       |                           |                           |        |
| Below $30k             | 13 (28%)                  | 12 (24%)                  | 0.31   |
| $30k-$100k             | 22 (47%)                  | 18 (36%)                  |        |
| Above $100k            | 12 (25%)                  | 20 (40%)                  |        |
Table 2

Psychosocial stressors associated with maternal race

| Stressor                                      | Non-Hispanic Black N=55 | Non-Hispanic White N=57 | P    |
|------------------------------------------------|--------------------------|-------------------------|------|
| **External Stressors**                        |                          |                         |      |
| Home Hardships Scale                          | 29.2±2.7                 | 29.5±2.4                | 0.59 |
| Food Insecurity (USDA)                        | 14.5±2.8                 | 13.55±2.8               | 0.04 |
| Neighborhood Satisfaction                     | 29.3±6.1                 | 32.1±4.9                | 0.02 |
| **Buffers of Stress**                         |                          |                         |      |
| Coping (State Hope Scale)                     | 18.5±3.2                 | 19.0±3.2                | 0.46 |
| Social Support (MOS-SSS)                      | 77.5±15.8                | 81.2±4.2                | 0.23 |
| Buffers of Stress Index                       | 147.1±16.1               | 152.8±13.0              | 0.04 |
| **Stress Enhancers**                          |                          |                         |      |
| Depression (CES-D)                            | 37.0±10.9                | 33.6±10.1               | 0.05 |
| **Perceived Stressors**                       |                          |                         |      |
| Cohen’s Perceived Stress Scale                | 27.6±7.5                 | 26.4±6.4                | 0.39 |
| Prenatal Distress Questionnaire               | 87.9±16.8                | 86.1±15.6               | 0.56 |
| Krieger Discrimination Scale                  | 11.3±1.7                 | 13.3±0.9                | <0.001 |

All values presented as means ± standard deviation
Table 3

Association of mean stress biomarkers with race

|       | Non-Hispanic Black (N=55) | Non-Hispanic White (N=57) | P  |
|-------|---------------------------|---------------------------|----|
| EBV   |                           |                           |    |
| 2nd tri | 5.41±0.3                  | 5.36±0.3                  | 0.40|
| 3rd tri | 5.40±0.3                  | 5.35±0.3                  | 0.41|
| CRP   |                           |                           |    |
| 2nd tri | 2.09±1.1                  | 1.59±0.9                  | <0.01|
| 3rd tri | 1.93±1.1                  | 1.51±1.0                  | 0.04|
| CRH   |                           |                           |    |
| 2nd tri | 1.64±2.6                  | 1.03±2.8                  | 0.24|
| 3rd tri | 0.43±2.2                  | 0.23±1.9                  | 0.62|
| ACTH  |                           |                           |    |
| 2nd tri | 2.94±0.5                  | 2.68±0.5                  | 0.01|
| 3rd tri | 2.85±1.05                 | 2.41±1.04                 | 0.03|

Analysis performed on log-transformed data with non-transformed means ± SD reported