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Racial Disparities in the Association Between Stress and Preterm Birth

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ABSTRACT

Background: High levels of maternal stress have been linked to preterm births. However, findings from previous studies are inconsistent due to the varied use of stress measures. This study examined the effect of maternal stress on preterm birth, using both psychosocial and physiological measures.

Methods: This study was conducted among 231 pregnant women enrolled during their first prenatal care visit. Presence of stress was assessed at enrollment using the Perceived Stress Scale (PSS) and Stressful Life Events Inventory (SLEI). Samples of maternal salivary cortisol were obtained during the first trimester and birth outcomes were ascertained at delivery. Multiple logistic regression was conducted to assess the association between stress and preterm birth.

Results: The majority of the study participants were Black, not married, less educated and low income. There was an association between cortisol level and preterm birth. Per 1µg/dL increase in cortisol level, the odds of preterm birth increased by 26%. The increase was accentuated in Blacks where a unit increase in cortisol level was associated with higher odds of preterm birth (29%).

Conclusions: Stress measures using PSS and SLEI did not reveal a statistically significant association with preterm birth. Health care and public health professionals should be aware of the association between increased cortisol level and preterm birth. Salivary cortisol may be a better predictor of preterm birth than PSS and SLEI.

Keywords: Stress; Preterm Birth; Birth outcome; Racial disparity; Premature Birth; Pregnancy

INTRODUCTION

Compared to many industrialized nations, the US continues to have one of the highest infant mortality rates (IMR) (Blencowe et al., 2012). Racial disparities are one of the primary factors contributing to the high infant mortality rates in the US. According to reports from the National Center for Health Statistics (NCHS), racial and ethnic disparities in infant death rates

are prominent with the IMR for Black infants (11.42 deaths/1,000 live births), totaling more than twice that of the national average of 6.05 deaths per 1,000 live births in 2011 (Hoyert & Xu, 2012; Mathews & MacDorman, 2013). A key factor in the problem of infant mortality is the prevalence of preterm birth (infants born at less than 37 weeks' gestation) (Martin, Hamilton, Menacker, Sutton, & Mathews, 2005).

According to the Institute of Medicine's recent publication, the proportion of preterm births has increased steadily over the past 10 years, with non-Hispanic African Americans experiencing the highest percentage (16.8%) compared to 10.5% for non-Hispanic Whites, and 11.6% for Hispanics (Behrman & Stith-Butler, 2007; Hamilton, Martin, & Ventura, 2012). In 2008, 35.4% of all infant deaths in the US were related to preterm birth (Mathews & MacDorman, 2012). Preterm-related infant mortality accounted for approximately 54% of the difference in infant mortality rates between non-Hispanic White and non-Hispanic Black women (Mathews & MacDorman, 2012).

In the past decade a number of studies have investigated maternal stress as a potential risk factor for preterm birth; however, the findings have largely been inconsistent (Bolten et al., 2011; Cha & Masho, 2013; Dunkel-Schetter & Glynn, 2011; Littleton, Bye, Buck, & Amacker, 2010). One potential reason for the inconsistencies in the literature may be the complex relationship between psychosocial stress and the underlying pathophysiologic mechanisms involving birth outcomes. Recent research purports a bidirectional relationship between maternal stress and susceptibility to preterm birth; however, the interaction between these mechanisms is not yet well understood (Wadhwa, Entringer, Buss, & Lu, 2011). Stress may affect pregnancy directly through the release of natural chemicals into the bloodstream, or indirectly by increasing negative health behaviors as a reaction to stressors (Copper et al., 1996; Law et al., 1993). Animal studies indicate that high stress levels during pregnancy are associated with poor birth outcomes (Welberg & Seckl, 2001); repeated exposure to stressors disrupts immune system regulation in pregnant animals, resulting in inflammatory responses and potential developmental issues in their offspring (Christian, 2012; Coe & Crispen, 2000; Golan, Lev, Hallak, Sorokin, & Huleihel, 2005; Rounioja et al., 2005). Women who perceive a great deal of stress, perhaps due to socioeconomic, behavioral, or environmental factors, are more likely to have preterm deliveries or give birth to low birth weight infants (Copper et al., 1996; Law et al., 1993; Tegethoff, Greene, Olsen, Meyer, & Meinlschmidt, 2010). Stress during pregnancy is also significantly associated with gestational hypertension, diabetes, and pre-eclampsia/eclampsia (Cha & Masho, 2013; Black, 2007; Hubel & Roberts, 2009; Leeners, Neumaier-Wagner, Kuse, Stiller, & Rath, 2007; Roberts & Hubel, 2004; Roberts & Lain, 2002).

Research also has shown that Blacks have a high prevalence of psychosocial stressors such as racism and other chronic environmental stressors, which could be factors for adverse birth outcomes (Behrman & Stith-Butler, 2007; Dominguez, Schetter, Mancuso, Rini, & Hobel, 2005; Lu & Halfon, 2003). Black women, by virtue of their "double-minority" status, are subject to a unique set of psychosocial stressors, which seem to operate independently of other known causes of stress (Rosenthal & Lobel, 2011; Pickett, Collins, Masi, & Wilkinson, 2005). Many studies have found large differences between racial and ethnic groups in terms of reported stressful life events and that Blacks had higher stress levels (Dominguez, Dunkel-Schetter, Glynn, Hobel, & Sandman, 2009; Lu & Chen, 2004). US-born Black women experienced significantly more stress related to racism over their lifetime compared to foreign-born Black women, suggesting that the source of stress is environmental rather than genetic (Dominguez et

al., 2009). Lu and Halfon (2003) identified stress as one of two problems what may explain disparities in infant mortality between Black and White women; in particular, they identified norepinephrine and cortisol as the natural chemicals responsible for triggering preterm deliveries. It is also indicated that racism, which can cause chronic stress, may prematurely age Black women, increasing their vulnerability to stress-related pregnancy complications (Gee, Walsemann, & Brondolo, 2012; Giurgescu et al., 2012; Geronimus, 1996; Hogue & Bremer, 2005; Holzman et al., 2009; Wallace & Harville, 2013). Moreover, disparities in social determinants lead to chronic stress which is responsible for poor outcomes.

It is important to note that women experience different levels of maternal stress depending on their dispositional coping styles in both the preconception phase and during gestation (Messer, Dole, Kaufman, & Savitz, 2005). Women also experience different types of stress, for instance perceived stress or stressful life events, which contribute to their overall psychosocial risk during pregnancy (Kingston, Heaman, Fell, Dzakpasu, & Chalmers, 2012). Prenatal stress may indirectly contribute to adverse birth outcomes through maladaptive coping behaviors, such as substance use, and negative attitude about the pregnancy (Messer et al., 2005; Zambrana et al., 1999). Stress can also increase susceptibility to infections which may complicate pregnancies (Lu & Halfon, 2003).

A major obstacle in understanding the effects of stress during pregnancy is the myriad of psychometric instruments used to quantify different types of stress. While these instruments are validated for use in the pregnant population, their ability to accurately reflect the physiological state is unclear. A recent meta-analysis found that psychological stress was only modestly associated with adverse birth outcomes, but unlikely to have any clinical significance (Littleton et al., 2010). However, this meta-analysis only included psychological measurements of stress, rather than physiological measures, such as salivary or serum cortisol. Our study builds upon the current literature by examining the effect of preconception stress on negative birth outcomes, specifically preterm birth, using both psychosocial and physiological measures. Additionally, the study examines racial differences in stress level and birth outcomes as a proxy for the differential impact of social determinants between races.

METHODS

A retrospective cohort study was conducted among 231 pregnant women enrolled during their first prenatal care visit. History of stress was assessed at enrollment and birth outcomes were obtained from medical records at delivery. The study was conducted at inner city prenatal care clinics from February 2010 through July 2012. The study included women who were 18 years or older, English-speaking, and initiating prenatal care during the first trimester of pregnancy (1-12 weeks of gestation). This study was reviewed and approved by the Virginia Commonwealth University Institutional Review Board.

Pregnant women who consented to participate completed a baseline self-administered survey. Data on demographic characteristics, reproductive history, lifestyle behaviors, and preconception stress were collected. Preconception and prenatal stress, with a focus on lifetime stress, and recent (past year) stress, were gathered using psychosocial stress scales (Chen, Grobman, Gollan, & Borders, 2011). The assessment battery included the following standardized and validated measures:

Perceived Stress Scale (PSS): The short version of the PSS was used to measure perceived stress (Cohen, Kamarck, & Mermelstein, 1983). PSS is the most widely used

psychological instrument for measuring perception of stress. The measure demonstrates strong internal consistency, with a Cronbach's alpha of 0.88. The scale is comprised of 10 items that ask subjects to rate how often they have perceived an event in their life, past year, and over the last month.

The Lobel and Zambrana Stressful Life Events Inventory (SLEI): The SLEI was used to measure frequency of lifetime and past year stressful life events (Zambrana et al., 1999; Lobel, 1994). The inventory included 24 major negative events that were categorized as a) serious illnesses or injuries, b) deaths among relatives or friends, c) deterioration in relationship between the participant and her partner, d) legal issues, e) financial or employment problems, and f) criminal matters pertaining to the participant, her partner, or family. This measure is also validated and reliable for this population (Dominguez et al., 2005; Lobel et al., 2008; Newton & Hunt, 1984; Newton, Webster, Binu, Maskrey, & Phillips, 1979).

Self-administered questionnaires were used to gather demographic data including age, education, employment, income, and marital status. Data on prior medical history such as diabetes, hypertension, heart disease, sexually transmitted diseases, and asthma were collected. The survey was also used to gather reproductive history including number of pregnancies, deliveries, miscarriages, intention of pregnancy, and prior history of low birth weight and preterm births. Questions about preconception health behaviors (multivitamin and folic acid use, regular exercise, regular medical checkup, availability of insurance and primary care provider, and date of last medical checkup) were also collected. Additionally, smoking, alcohol, and illicit drug use were assessed.

Finally, saliva samples were collected for cortisol assays that served as a biomarker for stress (Lobel et al., 2008). The procedure for collecting saliva involved provision of samples three times a day: at awakening, 30 minutes after waking (wake + 30), and 9:00 p.m. using a Salivette® kit. All samples were assayed using an enzyme immunoassay specifically designed for saliva analysis. The salivary cortisol determination was made through a commercially available high sensitivity competitive amino assay (Salimetrics, State College Pennsylvania).

After delivery, maternal prenatal health records and infant birth outcome data (miscarriage, live birth, gestational age, birth weight, number of prenatal visits, gestational diabetes, gestational hypertension, and incidence of pre-eclampsia) were abstracted from electronic medical records and hospital charts as needed. When electronic records were not available or were missing, manual chart abstraction was conducted. Initiation and frequency of prenatal care were used to calculate adequacy of prenatal care (Kotelchuck index) (Kotelchuck, 1994). The outcome of interest, preterm birth (PTB), was defined as delivery before 37 weeks' gestation. The PSS, SLEI, and average cortisol levels were analyzed as the main exposure variables. PSS, lifetime SLEI, past year SLEI, and cortisol levels were modeled as continuous and categorical variables. These variables were categorized into low, medium, and high tertiles. However, the categorical data was not robust and estimates for only the continuous variables were reported. Bivariate analysis was used to assess the relationship between the study variables with the outcome of interest. Multiple logistic regression analysis was conducted and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated controlling for potential confounding factors. Confounding factors were retained in the model if the variables produce a 10% change in the estimate. Separate logistic regression models were conducted for each stress measure of interest: cortisol level, perceived stress score, lifetime exposure to stressful life events, and year-long exposure to stressful life events.

Further, the analyses were stratified by race and the relationship between stress and preterm birth was examined among Blacks. In this study sample all preterm births, except one, occurred in Black women. Due to the small number, meaningful analysis to examine the relationship between stress and preterm birth in women who were White or another race was not possible. Therefore, the analyses were focused on Black women and the total study sample. All data analyses were conducted using SAS version 9.2.

RESULTS

The mean maternal age of study participants was 25.8 (SD=5.2) and 72% of the study sample was Black (Table 1). Preterm deliveries occurred in 14.3% of births. The majority of the study sample was not married (86.1%), had high school or less education level (61.2%), and earned less than $20,000 (79.0%). Over half (52.3%) were first-time mothers, three-quarter of the pregnancies were unintended, and over a quarter were smokers (27%). Table 2 shows that the incidence of preterm birth was higher among women who identified themselves as African Americans or Blacks, reported high school level education, earned less than $20,000, were uninsured, were primiparous or had 2 or more children, had history of prior preterm births, received adequate plus prenatal care, were smokers, and illicit drug users. Marital status, pregnancy intention, and physical abuse could not be assessed as confounders. None of the women who were married, whose pregnancy was intended, and who had history of physical violence experienced a preterm birth. The unadjusted analysis showed that preterm birth was significantly associated with race, maternal age, adequacy of prenatal care, and lifetime stressful life events.

Table 1. Characteristics of the Study Population

Characteristics	% or Mean (SD) Study Sample (N=182)
Mean Maternal age (SD)	25.8
Percent Black	72.0
Not married	86.1
Highest level of education	
Less than high school	26.4
High school or GED	34.8
Some college or greater	38.8
Annual household income < $20,000	79.0
Unemployed	40.9
Not Insured in year before pregnancy	61.0
Unintended Pregnancy	74.4
Parity	
No previous live births (n=93)	52.3
1 previous live birth (n=40)	22.5
≥2 previous live births (n=45)	25.3
Previous preterm birth	13.1
Alcohol use 3 months prior to pregnancy	59.6
Ever Illicit drug use	14.0
Physical Abuse prior to pregnancy	4.4
Smoker	27.8
Adequacy of Prenatal Care (Kotelchuck Index)	
Inadequate/Intermediate (n=50)	27.5
Adequate (n=79)	43.4
Adequate Plus (n=29)	15.9
Mean Cortisol Level (SD)	20.1 (6.8)
Mean Perceived Stress Scale Score (SD)	22.9 (7.0)
Mean Number of Lifetime Stressful Life Events (SD)	7.7 (6.8)
Mean Number of Year-long Stressful Life Events (SD)	4.9 (4.6)

Table 2 shows that the incidence of preterm birth was higher among women who identified themselves as African Americans or Blacks, reported high school level education, earned less than $20,000, were uninsured, were primiparous or had 2 or more children, had history of prior preterm births, received adequate plus prenatal care, were smokers, and illicit drug users. Marital status, pregnancy intention, and physical abuse could not be assessed as confounders. None of the women who were married, whose pregnancy was intended, and who had history of physical violence experienced a preterm birth. The unadjusted analysis showed that preterm birth was significantly associated with race, maternal age, adequacy of prenatal care, and lifetime stressful life events.

Table 2. Preterm Birth by Characteristics of the Study Population

Characteristics	Incidence of Preterm Birth	Chi-square (p-value) ‡
Race		8.80 (0.003)*
Black (n=131)	19.1%	
White/Other (n=51)	2.0%	
Highest level of education		3.90 (0.139)
Less than high school (n=47)	14.9%	
High school or GED (n=62)	21.0%	
Some college or greater (n=69)	8.7%	
Annual household income		3.80 (0.050)
< $20,000 (n=128)	15.6%	
≥ $20,000 (n=34)	2.9%	
Employment status		0.50 (0.477)
Unemployed (n=70)	12.9%	
Employed (n=101)	16.8%	
Insurance status in year before pregnancy		3.20 (0.072)
Not Insured (n=108)	18.5%	
Insured (n=69)	8.7%	
Parity		5.10 (0.079)
No previous live births (n=93)	15.1%	
1 previous live birth (n=40)	5.0%	
≥2 previous live births (n=45)	22.2%	
Previous preterm birth		0.10 (0.704)
No previous preterm birth (n=153)	14.4%	
Previous preterm birth (n=23)	17.4%	
Alcohol use 3 months prior to pregnancy		0.00 (0.835)
No (n=72)	15.3%	
Yes (n=106)	14.2%	
Smoking		0.00 (0.916)
Smoker (n=50)	14.0%	
Nonsmoker (n=130)	14.6%	
Adequacy of Prenatal Care		65.90 (<0.001)**
Inadequate/Intermediate (n=50)	4.0%	
Adequate (n=79)	5.1%	
Adequate Plus (n=29)	65.5%	
Cortisol Level Group		2.20 (0.341)
Low cortisol levels (n=40)	12.5%	
Medium cortisol levels (n=41)	17.1%	
High cortisol levels (n=40)	25.0%	
Perceived Stress Score		2.20 (0.340)
Low (n=63)	14.0%	
Medium (n=68)	9.8%	
High (n=59)	19.3%	
Stressful Life Events Lifetime		1.00 (0.599)
Low Exposure (n=55)	16.4%	
Medium Exposure (n=50)	18.0%	
High Exposure (n=61)	11.5%	
Stressful Life Events Year-long Exposure		0.10 (0.950)
Low Exposure (n=62)	16.1%	
Medium Exposure (n=54)	14.8%	
High Exposure (n=50)	14.0%	

‡Analysis compares preterm births with normal gestation births for each characteristic using chi-square test.
**p-value <0.01, **p-value<0.001*

Table 3 shows the crude and adjusted estimates for the total study sample and Black women. After adjusting for maternal age, education and adequacy of prenatal care, the mean cortisol level was significantly associated with preterm birth. Per 1 µ/dL increase in cortisol level, the odds of preterm birth increased by 26% in the study sample. When the analysis was conducted on Blacks, an increase in the odds of preterm birth was observed. Per unit increase in cortisol the odds of preterm increased by 29% among African American or Black women. Although PSS score was slightly higher for women who delivered preterm, this difference was not statistically significant. Similarly, the lifetime exposure to stressful life events was higher among women who delivered preterm, but not significantly so. There was also no significant difference in the past year exposure to stressful life events and preterm births.

Table 3. Association Between Stress Variables and Preterm Birth

	Total Study Population		**Black Population**	
	Odds Ratio [95% CI]			
Stress Measure	**Unadjusted**	**Adjusted†**	**Unadjusted**	**Adjusted†**
Cortisol	1.05 [0.99, 1.12]	1.26 [1.05, 1.50]*	1.12 [1.03, 1.22]*	1.29 [1.05, 1.58]*
PSS	1.01 [0.95, 1.08]	1.04 [0.95, 1.14]	1.01 [0.95, 1.07]	1.07 [0.97, 1.18]
SLEI Life	0.93 [0.86, 1.02]	0.87 [0.76, 1.00]	0.93 [0.85, 1.02]	0.86 [0.73, 1.00]
SLEI Year	0.97 [0.87, 1.07]	0.92 [0.76, 1.11]	0.94 [0.84, 1.07]	0.93 [0.76, 1.14]

†Adjusted for maternal age, education, adequacy of prenatal care
**p-value <0.05*

DISCUSSION

This study utilized a multidimensional approach to quantify stress in pregnant women, which included psychometric scales and biochemical measurements. Of the four stress measures, only the salivary cortisol predicted preterm birth in the study sample and this relationship was stronger among Black women. Consistent to other studies, this research also reported an association between higher levels of salivary cortisol and shorter gestation length (Diego et al., 2006; Entringer, Buss, Anderson, Chicz-DeMet, & Wadhwa, 2011; Himes & Simhan, 2011; Kramer et al., 2009; Voegtline et al., 2013). Studies have hypothesized that the release of stress hormones such as cortisol may lead to immune or inflammatory change which in turn leads to uteroplacental dysfunction leading to contraction, hence, preterm birth (Cha & Masho, 2013). Further, it is also hypothesized that stressors may increase negative health behaviors such as smoking and substance use which may lead to poor birth outcomes (Copper et al., 1996; Law et al., 1993).

While this study reported a statistically significant association between cortisol level and preterm birth, there was no statistical association with the psychosocial measures of stress. The reason for the lack of agreement between the biomarker and psychosocial measures is not clear. However, the lack of correlation between cortisol level and these psychosocial measures was also reported in recent studies (Himes & Simhan, 2011; Voegtline et al., 2013). Findings from

our study reinforced this distinction between perceived stress (psychosocial measures) and experienced stress (biomarker measure) when considering the impact of stress on fetal outcomes. Voegtline et al. (2013) suggested the importance of biochemical measures in determining the impact of maternal stress on fetal outcomes. Despite the disagreement between cortisol and psychosocial measurement of stress in recent studies, prior studies have reported a positive relationship between psychosocial measures of stress and poor birth outcomes (Wadhwa et al., 2011; Copper et al., 1996; Dominguez et al., 2005; Giurgescu et al., 2012; Dominguez et al., 2008; Chen et al., 2011; Newton & Hunt, 1984; Newton et al., 1979; Himes & Simhan, 2011; Woods, Melville, Guo, Fan, & Gavin, 2010).

Considering the study sample is predominantly African American or Black, psychosocial sources stemming from racism, discrimination, and lower socioeconomic status may have led to the increased level of stress observed among the Black population (Rosenthal & Lobel, 2011; Gee et al., 2012; Giurgescu et al., 2012; Holzman et al., 2009; Wallace & Harville, 2013; Dominguez et al., 2008; Lu & Chen, 2004; Dominguez et al., 2009; Zambrana et al., 1999). Psychosocial measures of stress capture one dimension of acute stress encountered at a level of the individual's perceived awareness. This may be distinct from chronic stress, which has been theorized to stem from the repeated and prolonged exposure to institutionalized oppression, discrimination, and racism; the individual may not be aware of the impacts of this chronic stress on her daily life. Chronic stress may not be adequately reflected in psychosocial measures which are designed to capture acute stress of which the individual is consciously aware. However, chronic stressors such as discrimination and racism were not able to be captured and evaluated in this study. However, the association between chronic stress and cortisol levels may be important for future research.

The nature of psychological stress and its exact mechanisms in relation to adverse birth outcomes are complex concepts and remain an important focus of multidisciplinary research efforts. The neuroendocrine pathways associated with the release of cortisol in response to stress have been established; however, differentials in maternal responses to stress and the relationship to preterm delivery are less clear (Kirschbaum & Hellhammer, 1994; Himes & Simhan, 2011; Kramer et al., 2009). This research shows that higher levels of cortisol are associated with preterm birth, especially among Black women.

The use of salivary cortisol and different forms of psychosocial assessments to measure stress was the main strength of this study. Salivary cortisol is a biochemical measurement of stress which is a less invasive method compared to other stress biomarkers such as maternal corticotrophin-releasing hormone or placental histopathology, which have been linked to preterm birth (Kramer et al., 2009). An additional strength of this study is its ability to examine the association of stress and preterm birth in a predominantly Black sample. Furthermore, the study examined a wide array of demographic and reproductive factors that may confound the association.

Despite its strengths this study has a number of limitations. The small sample size in this study may have contributed to the lack of significance between the psychosocial stress measures and preterm birth. Further, due to the small sample size, this study was unable to examine the association between stress and preterm births in Whites. As a result, the ability of this study to discern racial or ethnic differences on preterm birth is compromised. Although logistic regression analysis was not available for the White/other sample, prior literature has shown that

preterm birth is more common amongst the Black population so these results still present significant findings to the field.

CONCLUSION

Preterm births are a leading cause of infant mortality and the troubling racial disparities in adverse birth outcomes are a major problem facing public health. Determining the root causes of preterm birth and other adverse birth outcomes can help inform evidence-based medical practices and design community interventions. Finding from this study reported that increased levels of cortisol early in pregnancy predict preterm birth. Considering the relative consistency of this finding in previous studies, utilization of cortisol level to screen stressed women may not be farfetched. The findings of this study may have significant clinical and public health relevance. However, future studies with larger sample size are needed to confirm this association. Additionally, this study should be replicated in racially diverse populations to assess racial and ethnic differences in the association between stress and preterm birth.

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