ARTICLE

Maternal perceived stress and the increased risk of preterm birth in a majority non-Hispanic Black pregnancy cohort

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OBJECTIVE: To determine whether perceived stress is associated with preterm birth (PTB) and to investigate racial differences in stress and PTB.
STUDY DESIGN: A secondary analysis of a prospective cohort study of 1911 women with singleton pregnancies examined responses to psychosocial stress questionnaires at 16–20 weeks of gestation.
RESULTS: High perceived stress (19%) and PTB (10.8%) were prevalent in our sample (62% non-Hispanic Black). Women with PTB were more likely to be Black, have chronic hypertension (cHTN), pregestational diabetes, and higher BMI. Women with high perceived stress had more PTBs than those with lower stress (15.2% vs. 9.8%), and stress was associated with higher odds of PTB (aOR: 1.55, 95% CI: 1.09–2.19).
CONCLUSION: The significant association between high perceived stress and PTB suggests that prenatal interventions to reduce maternal stress could improve the mental health of pregnant women and may result in reduced rates of PTB.

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INTRODUCTION

Preterm birth (PTB), a birth that occurs prior to 37 completed weeks of gestation, is a major public health issue in the United States that affects ~10% of births and is responsible for one-third of infant deaths [1], 50% of long-term neurological sequelae [1], and $26.2 billion in costs annually [2]. Epidemiologic risk factors for PTB include maternal smoking, medical comorbid conditions, and self-reported non-Hispanic Black race/ethnicity. Given that race is a social, not a biological or genetic construct [3], it is critical to understand the individual and societal factors such as stress that may lead to increased risk of PTB among Black pregnant women in the United States.

Psychosocial stress refers to the cognitive appraisal of the discrepancy between a demand and an individual's ability to meet it. In US [4–6] and international samples [7], maternal prenatal stress has been found to be associated with PTB as well as other poor birth outcomes including low birth weight, and intrauterine growth restriction. While it has been well-established that Black women have an increased risk to PTB compared to White women, studies have not routinely focused on the contribution of maternal prenatal stress to the racial differences in birth outcome. Stress can lead to physiologic changes such as increases in corticotrophin-releasing hormone (CRH), prostaglandins, and inflammatory cytokines that may result in uterine contractions and/or spontaneous PTB [8–10]. Despite plausible biological pathways implicating stress in PTB, studies examining its impact have been equivocal [11–14] likely due to the incomplete understanding of the association between perceived psychosocial stress and birth outcomes [15].

While the underlying pathophysiology of PTB remains incompletely understood, PTB can be dichotomized as either medically-indicated (mPTB) secondary to conditions in either the pregnant woman or the fetus, or as spontaneous (sPTB) occurring after spontaneous rupture of membranes or preterm labor. sPTB accounts for over two-thirds of all PTBs [1, 16]. While there are some data suggesting inflammatory processes [17], maternal psychological factors [18], diet and/or the microbiome [19] play a role in sPTB, the precise pathogenesis of sPTB and how these factors contribute to sPTB are not elucidated and directed therapeutics are lacking. Similarly, neuroendocrine and inflammatory processes, such as those associated with stress and maternal lifestyle and behavioral processes, may contribute to the medical etiology of some mPTBs including gestational hypertension and diabetes [20–23].

The neuroendocrine milieu of pregnancy is unique, with dramatic alterations in HPA axis regulation and neurosteroid production. Pregnancy represents a state of heightened cortisol and CRH production where cortisol stimulates the release of placental CRH and both play a role in fetal maturation and the "parturition clock." It has been suggested that maternal psychosocial distress is related to disruptions in typical cortisol trajectories during gestation [24], and numerous studies have indicated that placental CRH production remains sensitive to maternal psychological stress [25], both of which are likely to increase the risk of PTB [26–28].

The PTB rate in the United States has worsened for a fourth year, from 9.6% in 2015 to 10.0% in 2018 when data was last

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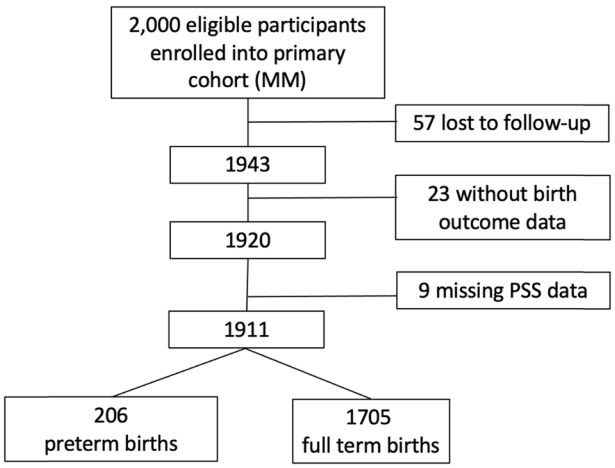

Fig. 1 Study enrollment flow chart.

available [29]. This upward trend is largely due to increases in PTB among non-Hispanic Black women [29]. Compared to non-Hispanic White women, Black women's risk of PTB was 1.5 times higher (14.13% vs. 9.09%) [1, 29]. The reason for this persistent disparity in pregnancy outcome is not known, but hypothesized to be related to the well-known racial disparities in social determinants of health including systemic racism. It has been well documented that Black women report higher rates of perceived stress, depression, and other mental illness during pregnancy compared to White women, regardless of income [30–38]. These racial disparities are not explained by lack of health care access, socioeconomic status, or genetics [33, 35, 39, 40].

While psychosocial stress, depression, and other general distress are common during pregnancy [31, 35], the extent to which stress is associated with PTB, especially in largely Black pregnancy cohorts is not well studied. Thus, the objectives of this study were to quantify associations of perceived stress in pregnancy with PTB and its subtypes (sPTB and mPTB) in a large prospective, majority Black pregnancy cohort wherein we hypothesized that higher self-reported stress scores would be associated with PTB. We also sought to explore racial differences in stress and PTB between non-Hispanic Black and White women; we hypothesized that we would find higher reports of stress among Black women, and that this would be associated with PTB.

MATERIALS AND METHODS

Study setting

This study was a planned secondary analysis of a cohort of 2000 women enrolled from December 2013 through February 2017 [41]. Eligibility for the parent study was restricted to pregnant women with a gestational age of 16^0–20^6 weeks at the time of the first study visit. Exclusion criteria included: (1) major fetal anomaly, (2) HIV+, (3) history of organ transplant, (4) chronic steroid use, (5) enrollment into the study during a previous pregnancy, or (6) multiple gestations (mechanisms leading to PTB in twins is different from singletons). Patients were enrolled at three prenatal care clinics at the Hospital of the University of Pennsylvania. Two follow-up visits occurred between 20^0–24^6 and 24^0–28^6 weeks GA. Enrollment and follow-up visits occurred at regularly scheduled prenatal visits approximately every 4 weeks until the 3 study visits were completed. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at the University of Pennsylvania; all participants gave consent (IRB #818914).

Covariate and exposure (perceived stress) data

Maternal demographics, obstetric history, and pregnancy outcomes were abstracted from the Electronic Medical Record. Perceived stress was measured using the Cohen's Perceived Stress Scale (PSS-14), a 14-item survey [42]. Although the PSS-14 is not specific to pregnancy, it has been validated and widely used during pregnancy [42–45]. According to previously validated measurement data, women were considered to have high perceived stress if they scored above a cutoff score of 30 on the PSS-14 [46]. Participants completed surveys at each of the three study visits, but we used the responses from the initial study visit (16–20 weeks of gestation) because it had the most complete data and previously published data supports the role of earlier prenatal stress in contributing to the risk of PTB [47].

Cohort and imputations

A total of 2982 pregnant women were approached for the study. Among those approached, 982 (33%) declined, 57 were lost to follow-up, 23 were missing birth outcomes, and 9 had no PSS-14 data from any visit (Fig. 1). The final analytic cohort included 1911 women with original or derived PSS-14 scores and birth outcome information. Of these 1911 women, 103 were missing PSS-14 scores at the initial study visit (16–20 weeks of gestation). We imputed the initial visit PSS-14 score in one of two ways. For the 89 women with incomplete scales, but missing fewer than three questions, we averaged the responses from the remaining questions to determine the final score (scaling). If a woman were missing an entire questionnaire but completed it at a following visit, we used the score from that questionnaire ($n = 14$).

Outcome—preterm birth (PTB)

PTB was defined as delivery at <37 weeks. Secondary outcomes of sPTB and mPTB were adjudicated by a maternal–medicine physician (ME) to confirm the presence of preterm rupture of membranes or preterm labor to designate a PTB as sPTB and to identify the indication for mPTB [41].

Data analysis

Bivariate analysis was performed using Pearson chi-square tests for categorical variables, and two-sided *t* tests for continuous variables. Covariates were considered for inclusion in the final model if they were hypothesized a priori to be clinically relevant, and were retained if they substantially (>10%) modified the association of interest. We utilized multivariable logistic regression models to examine the association between high perceived stress at 16–20 weeks of gestation (PSS-14 ≥30) and PTB. In secondary analyses, we examined the association between high perceived stress and specific type of PTB in separate models (sPTB and mPTB). To assess whether a "dose-response" effect may exist and to further justify our findings, we examined the association between quartiles of PSS-14 scores and PTB, where Q1 represents the lowest scores and Q4 the highest. Additionally, we assessed the association between quartiles of PSS-14 score and PTB after stratifying by race. As a sensitivity analysis, we assessed the association in the original (non-imputed) cohort, which included only women with complete PSS-14 scores at the initial visit. Odds ratios and 95% confidence intervals (CIs) for PTB associated with high PSS-14 at this study visit were obtained. Due to differences in stress in this cohort by race and differences in PTB rates by race [32], we added stress to a model of race and PTB to examine whether stress might mediate racial disparities in PTB in this cohort. We also performed race stratified models and tested for interaction between race and stress on the outcome of PTB. Statistical analyses were conducted using STATA® 14 software.

RESULTS

Demographics

Demographics, overall and by PTB status, are presented in Table 1. A total of 206 (10.8%) of the 1,911 women experienced a PTB. Maternal characteristics were compared between PTB and term births. Non-Hispanic Black women represented 62.0% of the sample, and the average age was 28.5 years, pregnant individuals with a PTB were more likely to be non-Hispanic Black, have an overweight or obese BMI, chronic hypertension (cHTN), and pregestational diabetes (Table 1).

PSS-14

Mean PSS-14 score was 22.3 (SD 8.0) for term births and 24.2 (SD 7.8) for PTBs ($p = 0.001$). Among women with high perceived stress (PSS-14 ≥30), the PTB rate was 15.2% compared to 9.7% among women with lower stress scores ($p = 0.003$) (Table 1). In the unadjusted

Table 1. Characteristics of 1911 participants in *Motherhood and Microbiome* cohort with perceived stress data by preterm birth.

Maternal characteristics	All ($n = 1911$)	Term birth ($n = 1705$)	Preterm birth ($n = 206$)	*P* value
Age				0.700
<20	123 (6.4)	111 (6.5)	12 (5.8)	
20–34	1448 (75.8)	1287 (75.5)	161 (78.2)	
>34	340 (17.8)	307 (18.0)	33 (16.0)	
BMI[a]				0.008
<25	648 (33.9)	596 (35.0)	52 (25.2)	
25–29	524 (27.4)	468 (27.4)	56 (27.2)	
≥30	719 (38.0)	624 (37.0)	95 (46.8)	
Race/ethnicity				
Non-Hispanic Black	1184 (62.0)	1036 (60.8)	148 (71.8)	0.005[b]
Non-Hispanic White	521 (27.3)	480 (28.2)	41 (19.9)	
Hispanic/Latina	79 (4.1)	69 (4.1)	10 (4.9)	
Non-Hispanic Asian/other	127 (6.7)	120 (7.0)	7 (3.4)	
Gestational age at delivery in weeks (Mean, SD)[c]	38.2 (3.0)	39.0 (1.2)	31.9 (5.1)	<0.001[d]
Obstetric history				<0.001
Nulliparous	840 (44.0)	759 (44.5)	81 (39.3)	
Multiparous with term births	860 (45.0)	791 (46.4)	69 (33.5)	
Prior PTB	211 (11.0)	155 (9.1)	56 (27.2)	
Psychiatric history[e]	309 (16.2)	268 (15.7)	41 (19.9)	0.123
CES-D ≥16 V1[f, g]	561 (31.8)	488 (30.9)	73 (38.8)	0.028
PDQ ≥17 V1[f, h]	390 (22.5)	344 (22.3)	46 (24.1)	0.570
Medicaid insurance	990 (51.8)	875 (51.3)	115 (55.8)	0.222
Single marital status	1254 (65.6)	1116 (65.5)	138 (67.0)	0.661
Chronic hypertension	111 (5.8)	83 (4.9)	28 (13.6)	<0.001
Tobacco use in pregnancy[i]	171 (9.0)	146 (8.6)	25 (12.2)	0.087
Pregestational diabetes	44 (2.3)	33 (1.9)	11 (5.3)	0.002
PSS-14 ≥30	363 (19.0)	308 (18.1)	55 (26.7)	0.003
PSS-14 (Mean, SD)	22.5 (7.8)	22.3 (8.0)	24.2 (7.8)	0.001[d]

Data presented as *n* (col %), Chi-square *p* value unless otherwise indicated.
PTB Preterm birth (birth <37 weeks gestational age), *PSS* Cohen's Perceived Stress Scale (14 items), *V1* Visit 1, *V2* Visit 2, *V3* Visit 3, *CES-D* The Center for Epidemiologic Studies Depression Scale, *PDQ* prenatal distress questionnaire.
[a]$n = 20$ missing BMI.
[b]Fisher's exact test.
[c]$n = 26$ missing gestational age at delivery.
[d]Two-sided *t*-test.
[e]Reported psychiatric health history in Electronic Medical Record problem list.
[f]Defined as screened positive at individual visit.
[g]$n = 145$ missing CES-D score at V1.
[h]$n = 175$ missing PDQ at V1.
[i]$n = 4$ missing tobacco use.

logistic regression model, there was a positive, significant association between PSS-14 ≥30 and PTB (OR: 1.65, 95% CI: 1.18–2.30). The association remained significant after adjusting for race, BMI, Medicaid insurance, obstetric history, pregestational diabetes, and cHTN (aOR: 1.47, 95% CI: 1.03–2.08) (Table 2). Additionally, we found an increasing adjusted odds ratio for each quartile compared to Q1, with participants in Q4 having the highest odds of PTB (aOR: 1.50, 95% CI: 0.98–2.28) (Table 3). Results were similar in complete-case analysis (Supplementary Table 1).

Phenotypes of PTB

The different pathogeneses of PTB phenotypes led us to build separate models examining the association between high PSS-14 score and sPTB and high PSS-14 score and mPTB. We found significant positive associations between both high stress and sPTB (OR: 1.55, 95% CI: 1.01–2.37) and high stress and mPTB (OR: 1.81, 95% CI: 1.11–2.96) in crude models. In both models, the associations became non-significant after adjustment for race, BMI, Medicaid insurance, obstetric history, pregestational diabetes, and cHTN (Supplementary Table 2).

Race/ethnicity, perceived stress, and PTB

A higher proportion of non-Hispanic Black women (24.7%) had a PSS-14 score ≥30 than White women (7.7%) ($p < 0.001$). Black women also had higher rates of PTB (12.5%) compared to White women (7.9%) ($p = 0.007$). However we did not detect PSS-14 score to be a significant mediator of the race-PTB association. The Black-White disparity in PTB in adjusted models without PSS-14 was OR = 1.76, 95% CI: 1.13–2.76). When PSS-14 ≥30 was added to model, the effect estimate was unchanged (aOR = 1.64, 95% CI: 1.05–2.58) (Table 4). However, there were only four White women with both high PSS-14 and PTB.

Table 2. Association between high perceived stress (PSS-14 ≥30) and preterm birth ($n = 1911$).

Perceived stress levels	Model 1	Model 2[a]	Model 3[a]	Model 4[a]
PSS-14 ≥30	1.65 (1.18–2.30)	1.56 (1.10–2.21)	1.50 (1.06–2.12)	1.47 (1.03–2.08)
PSS-14 <30	Ref.	Ref.	Ref.	Ref.

Model 1: Crude association between high PSS and PTB.
Model 2: Adjusted for Medicaid insurance, obstetric history, and BMI.
Model 3: Model 2 + race/ethnicity.
Model 4: Model 3 + pregestational diabetes, and chronic hypertension.
[a]$n = 20$ missing BMI.

In models restricted to non-Hispanic Black women, those with PSS-14 ≥30 had significantly higher odds of PTB compared to those with lower perceived stress scores (OR = 1.50, 95% CI: 1.03–2.19) and this association remained significant when adjusted for Medicaid insurance, obstetric history, BMI, pregestational diabetes, and cHTN (aOR = 1.59, 95% CI: 1.08–2.34). Among Non-Hispanic White women, high stress was not significantly associated with increased odds of PTB (aOR 1.10, 95% CI: 0.34–3.55). However, the interaction between race and high stress was not significant ($p = 0.84$). For maternal characteristics by race, see Supplementary Table 3.

DISCUSSION

In a large, majority non-Hispanic Black cohort of pregnant women, we found that high perceived stress during pregnancy is associated with PTB. Overall, the prevalence of above threshold scores on the PSS-14 were substantially higher among Black women compared to non-Black women in our cohort, and Black women were more likely to experience a PTB. Among non-Hispanic Black women, those with higher reported stress were 1.5 times more likely to have a PTB. This finding suggests that stress may have an additive effect in already vulnerable populations which may influence biological processes such as parturition and is consistent with the "weathering" hypothesis which suggests that chronic exposure to social and economic disadvantage leads to accelerated decline in physical health outcomes and could partially explain racial disparities in a wide array of health conditions [48–50], including PTB [51].

The precise biological mechanisms linking perceived stress and PTB remain unclear. Investigations into the associations between biomarkers of stress, self-reported stress and support, and sPTB have been equivocal [11–15]. While some work has found no association between PTB and biomarkers including maternal serum cortisol, CRH, and adrenocorticotrophic hormone and reports of maternal psychosocial stress and perceived support [19], others have found that stress/distress may affect inflammatory cytokines, which were associated with PTB [52]. Further research exploring a more comprehensive assessment of maternal immune responses to stress and depression throughout pregnancy may yield additional insight into these associations. While differences in psychosocial stress alone are insufficient to explain racial disparities in PTB [38], understanding the mechanisms linking psychosocial distress before and during pregnancy to PTB among Black women may be critical to improving birth outcomes among Black women.

As high rates of stress and depression (which may contribute to perceived stress) have been reported in both pregnant and non-pregnant Black women, our findings of elevated levels of stress in pregnant non-Hispanic Black women may not be specific to pregnancy [48, 52–54]. However it is likely that pre-pregnancy stress is associated with prenatal stress. This study cannot determine if pregnancy modifies or exacerbates that level of stress.

This study has some limitations. The 3 time points spanned only a 12-week time period within the second trimester of pregnancy. Psychological conditions might change over a greater period of time than 12 weeks, and stress may increase as pregnancy progresses. Our data cannot determine whether PTB is associated with transient depression and psychological distress that resolved prior to the first visit assessment or increased after it. Further, this cohort included women who presented for a prenatal visit prior to 20^{6} weeks. Patients who present >$20^{6/7}$ weeks of pregnancy might be at a higher risk for both stress and PTB. This study did not account for other psychosocial (i.e., experience of discrimination or racism; or trauma) or genetic factors that contribute to stress and/or the outcome of PTB. While we gathered medical record data on psychiatric history, this was based on problem list designation which does not differentiate between current and past disorders. These data relies on individual providers adding the diagnosis to the medical record problem list which may result in an underestimate of psychiatric disorders in this sample. Similarly, we did not assess for participant substance use disorders, other than tobacco use in pregnancy. Imputed data carries its own limitations, however our results were similar in the non-imputed, complete-case analysis. Although sPTB and mPTB were combined in the primary model, secondary analyses show that high stress may act similarly on PTB regardless of phenotype. Lastly, while we hypothesized a mediating effect of perceived stress on the relationship between race and PTB this study was ultimately underpowered to detect this effect as only four White women with high PSS-14 score had a PTB. Similarly, the study was underpowered to detect an interaction between race and stress.

Strengths of the study include that it is a large, prospective cohort, with well-phenotyped cases of PTB and a high proportion of Black women, who are historically understudied but at higher risk for PTB. Further, this study used a well-validated measure to assess psychosocial wellbeing. Finally, our study confirmed that the PSS-14 is an easily administered tool that can be used during pregnancy to quickly identify women at highest risk for heightened distress that may warrant the further attention of a mental health provider.

CONCLUSIONS

In this study, we demonstrate associations between maternal perceived stress and PTB. Specifically, perceived stress was significantly associated with PTB for all women. Although this study was not powered to detect the role of stress as a mediator between race and PTB, we did confirm previous findings suggesting that Black women report more perceived stress than non-Hispanic White women [55]. These results suggest that there is utility in screening and referral to evidence-based mental health intervention for stress that could potentially modify the PTB rate, which is particularly important for Black women who have excess PTB risk [56]. The American College of Obstetricians and Gynecologists recommends screening for prenatal depression and psychosocial stress at least once during pregnancy using a standardized, validated tool to help prevent severe postpartum depression, impaired mother-infant interactions, suicide, and infanticide [57]. In the last decade, an increased interest in prevention and treatment of postpartum depression has motivated perinatal screening and referral to treatment, however perceived stress and depression are distinct constructs [55]. Measuring

Table 3. Association between quartiles of Perceived Stress Scale (PSS-14) and preterm birth ($n = 1911$).

Quartiles of PSS-14	Preterm birth *n* (%)[a]	Crude OR (95% CI)	aOR[b] (95% CI)
Q1 (2–17) ($n = 546$)	48 (8.7)	Ref	Ref
Q2 (18–22) ($n = 430$)	39 (9.1)	1.03 (0.66–1.61)	0.99 (0.63–1.56)
Q3 (23–28) ($n = 485$)	55 (11.3)	1.33 (0.88–2.00)	1.24 (0.81–1.90)
Q4 (29–55) ($n = 450$)	64 (14.2)	1.72 (1.16–2.56)	1.50 (0.98–2.28)

[a]Chi-Square test, $p = 0.026$.
[b]Adjusted for Medicaid insurance, obstetric history, BMI, race/ethnicity, pregestational diabetes, and chronic hypertension.

Table 4. Association of race and preterm birth, unadjusted, covariate-adjusted, and additionally adjusted for high perceived stress ($n = 1705$).

Race	Model 1	Model 2	Model 3
Non-Hispanic Black	1.67 (1.16–2.40)	1.76 (1.13–2.76)	1.64 (1.05–2.58)
Non-Hispanic White	Ref	Ref	Ref

Model 1: Crude association between non-hispanic black race and PTB.
Model 2: Adjusted for Medicaid insurance, BMI, obstetric history, pregestational diabetes, and chronic hypertension (cHTN).
Model 3: Model 2 + high PSS ≥30 at V1.

depression alone may overlook a woman's level of perceived stress, which may be associated with poor pregnancy outcomes, including PTB. While stress is related to, and contributes to, depression and anxiety, the current findings suggest that even non-pathological experiences of stress are associated with significant health risks to both mother and child. Given that perceived stress may be a modifiable variable, future research should investigate stress management interventions for pregnant women.

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SLK: conceptualization, writing—original draft, review, and editing. VMR: data curation, investigation, project administration, and writing—original draft. CM: formal analysis, investigation, and methodology. MAE: conceptualization, funding acquisition, project administration, resources, supervision, writing—review and editing. HHB: conceptualization, methodology, writing—review and editing.

COMPETING INTERESTS

The authors declare no competing interests.

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