

What Causes Racial Disparities in Very Preterm Birth? A Biosocial Perspective

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Very preterm birth (<32 weeks' gestation) occurs in approximately 2% of livebirths but is a leading cause of infant mortality and morbidity in the United States. African-American women have a 2-fold to 3-fold elevated risk compared with non-Hispanic white women for reasons that are incompletely understood. This paper reviews the evidence for the biologic and social patterning of very preterm birth, with attention to leading hypotheses regarding the etiology of the racial disparity. A systematic review of the literature in the MEDLINE, CINAHL, PsycInfo, and EMBASE indices was conducted. The literature to date suggests a complex, multifactorial causal framework for understanding racial disparities in very preterm birth, with maternal inflammatory, vascular, or neuroendocrine dysfunction as proximal pathways and maternal exposure to stress, racial differences in preconceptional health, and genetic, epigenetic, and gene-environment interactions as more distal mediators. Interpersonal and institutionalized racism are mechanisms that may drive racially patterned differences. Current literature is limited in that research on social determinants and biologic processes of prematurity has been generally disconnected. Improved etiologic understanding and the potential for effective intervention may come with better integration of these research approaches.

continental population groups; health status disparities; pregnancy complications, infectious; premature birth

Abbreviations: CRH, corticotropin-releasing hormone; VPT, very preterm.

INTRODUCTION

Premature birth is an intermediate cause of infant mortality and morbidity. It is intermediate in that birth too early in gestation results from proximate dysfunction in the uterine milieu; it is likely causal in that the harm to the fetus or infant is not solely from these dysfunctions but also from the consequences of shortened gestation on respiratory and neurologic function in the extrauterine world. While prematurity is a continuum, with the whole population of births before 37 weeks' gestation experiencing some increased risk compared with term birth at 37 weeks or more, it is the extreme of the distribution, very preterm (VPT) birth (defined here as birth before 32 weeks' gestation), that accounts for the lion's share of harm attributable to prematurity. VPT birth occurred in 20.3 of 1,000 US births in 2006 (1). This relatively small percentage of births accounts for a third of all infant deaths, 67% of neonatal mortality (2, 3), and a significant prevalence of acquired developmental disabilities such as cerebral palsy, mental retardation, and less severe cognitive disability (4, 5).

While VPT birth is a poor outcome for any pregnancy, African-American women experience nearly 3 times the risk of VPT birth when compared with non-Hispanic white women (1). This magnitude of disparity persists for the closely related outcome of very low birth weight (<1,500 g) even among college-educated black women married to college-educated black men, who are delivering their first- or second-born infant in their twenties or thirties after having received prenatal care beginning in the first trimester (6).

This long-observed pattern of correlation between the social construct of race and the biologic outcome of VPT birth has been discussed and studied for decades in 2 largely separate literatures: social determinants of health and biologic/clinical processes resulting in prematurity. In this review, we seek to synthesize these bodies of literature, with particular attention to linkages between the 2, with the intention of advancing a research agenda to understand and diminish the population health burden embodied by the racial disparity in VPT birth.

To accomplish this goal, we systematically searched MEDLINE, CINAHL, PsycINFO, EMBASE, and the

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Cochrane Database using the Medical Subject Heading (MeSH) term “premature birth” as well as “preterm” and “premature” as keywords and crossing them with the MeSH term “continental population groups” or “race” as a keyword. This search resulted in 1,459 citations between 1960 and February 2009. With the stated goal of understanding the etiology of the black-white racial disparities in preterm birth, each author independently selected relevant abstracts and papers, with disagreement favoring retaining the additional citation. References from selected citations were also reviewed to identify other relevant papers. An initial inductive review of relevant literature resulted in a general conceptual framework. With this framework, we reviewed the entire list again, and relevant papers were examined and coded according to the framework.

The inductive review highlighted 2 important caveats worth noting: the choice of perinatal outcomes and measure is important; and the conceptual framework in play can drive the inferences from any given study. Each is briefly discussed in the following sections.

MEASURES AND OUTCOMES

Perinatal epidemiologists have described many similarities (and some differences) across pregnancy outcomes such as low birth weight (<2,500 g), very low birth weight (<1,500 g), preterm birth (<37 weeks), and VPT birth (variably defined as <34, <32, or <28 weeks' gestation). The many similarities in risk factors for these outcomes make it tempting to lump the entire body of literature together, but the differences are important to note. Birth weight as an outcome is very reliably measured in vital statistics data sets, but the common low birth weight definition of <2,500 g mixes data for preterm and growth-retarded babies and is not likely a causal intermediary between proximate insult and subsequent mortality or morbidity (7, 8). Although the metric of gestational age more directly connects intrauterine processes to extrauterine consequences, it is notoriously challenging to measure well, particularly in commonly used vital statistics data sets, and particularly when comparing across demographic groups such as race or socioeconomic status. Specifically, there is evidence for differential misclassification of gestational age calculated from last menstrual period for poor and minority women, although use of ultrasound dating has reduced this error (9).

For this review, we preferentially sought studies using ultrasound-based dating or data-cleaning approaches that reduce misclassification (10, 11). Because of the high correlation between the outcome very low birth weight (<1,500 g) and VPT birth (the gestational ages of only 9.8% of black births and 12.8% of white births classified as <1,500 g were more than 32 weeks (12)), we included studies using either outcome to address our primary aim. Because so much more literature uses the broader categories of low birth weight (<2,500 g) and preterm birth (<37 weeks), we reference this as suggestive of hypotheses, acknowledging that these less extreme outcomes may be etiologically and epidemiologically distinct from VPT birth. For the remainder of this review, we specifically refer to studies that explicitly or

implicitly test a hypothesis for explaining the observed association of black/white race with either very low birth weight or VPT birth as an outcome. Those studies are also summarized in Table 1, indicating, where possible, the mediating pathway evaluated.

CONCEPTUAL FRAMEWORK

The conceptual framework used for investigating the etiology of a disparity in VPT birth affects what is included as potential causal agents. The bulk of the reviewed literature sought to explain the observed association between the socially constructed category of race and the outcome of prematurity (represented by the dotted line in Figure 1) as mediated by socioeconomic status, individual behaviors, and/or genetics. Residual association after statistical control for proxies of socioeconomic status or known risk factors has often been assumed to illuminate the role of genetic predisposition in explaining the disparity (13, 14). However, it has become increasingly clear that prematurity is a complex disease, and attribution of residual variation to an unmeasured variable may not adequately represent this complexity. Our initial review of the literature gave rise to an alternate conceptual framework explaining the observed association between phenotypic or socially constructed race and the outcome of VPT birth (Figure 2).

Briefly, this conceptual framework suggests that 3 primary proximate biologic pathways mediate the racial disparity in VPT birth: uteroplacental vascular dysfunction, placental and maternal hypothalamic-pituitary-adrenal-axis dysfunction, and maternal-fetal inflammation (refer to Challis (15), Lockwood and Kuczynski (16), and Behrman and Butler (17) for further discussion of these biologic pathways). At the most distal end of the framework, there are 3 possible linkages between phenotypic race and subsequent biologic variations: the latent variable institutionalized racism, which explains the racial differences in a wide variety of socioeconomic exposures; interpersonal racism; and possibly a correlation between phenotypic race in the United States and genotype or epigenetic gene expression. Between these distal and proximal nodes are a wide variety of hypothetical intermediary pathways. To our knowledge, no study to date has attempted to describe the entirety of this complexity. However, we identified 3 frequently hypothesized intermediaries between race and VPT birth, indicated in light grey in Figure 2: maternal experiences of psychosocial stress, periconceptional maternal health status, and genetic predisposition or gene-environment/epigenetic modification of risk. We use these 3 nodes to structure the review of evidence for various pathways.

THE STRESS HYPOTHESIS

The stress hypothesis for perinatal outcomes tends to focus on 2 types and time periods of psychosocial stress: acute stress during pregnancy or life-course exposure to stressors prior to conception. Acute perinatal stressors may be pregnancy-related anxiety or major life events such as divorce, major illness, or death of a loved one. Preconceptional

Table 1. Summary of Studies Evaluating Intermediate Variables in the Association Between Black/White Race and Occurrence of Very Preterm Birth or Very Low Birth Weight

Author, Year, (Reference No.)	Outcome	Pathway ^a	Results
Simhan, 2003 (156)	VPT birth ^b	Genotype/epigenetics	The interleukin-6 polymorphism was protective against VPT birth in white women, but single-nucleotide polymorphism was not present in black women cases or controls in the study.
Catov, 2007 (138)	VPT birth ^b	Preconceptional health	Periconceptional multivitamin use was protective against VPT birth and was less prevalent among black women than white women.
Ehrenthal, 2007 (102)	VPT birth ^c , VLBW ^d	Preconceptional health	Although black women had a higher prevalence of preconceptional hypertension and diabetes than white women did, control for preconceptional health status did not appreciably reduce the racial disparity.
Khoshnood, 1998 (136)	VLBW ^d	Preconceptional health	Black women and white women with an IPI of <6 months had a higher risk of VLBW than those with an IPI of ≥12 months; black women had a higher prevalence of an IPI of <6 months than white women did.
Berg, 2001 (163)	VLBW ^d	Preconceptional health; substance abuse; SES; acute, chronic, or early-life stress	A significant racial difference in the risk profile for VLBW was found. SES markers were associated with white, but not black, VLBW. Only unmarried status, smoking, and no vitamin use during pregnancy were associated with VLBW for black women.
Andrews, 2006 (117)	VPT birth ^c	Preconceptional health, inflammation	Interconceptional antibiotic treatment in high-risk black women and white women did not change the risk of VPT birth.
Catov, 2007 (164)	VPT birth ^e	Preconceptional health, inflammation	Early-pregnancy elevated C-reactive protein and dyslipidemia levels double the risk of VPT birth for black women and white women (adjusted for but not stratified on race).
Jeffcoat, 2001 (53)	VPT birth ^c	Preconceptional health, inflammation	Periodontitis at 24 weeks increases the risk of VPT birth 7-fold and is more prevalent in black women than white women.
Offenbacher, 2006 (114)	VPT birth ^c	Preconceptional health, inflammation	Progression of periodontal disease during pregnancy doubles the risk of VPT birth for black women and white women (adjusted for but not stratified on race).
Dunlop, 2008 (120)	VLBW ^d	Preconceptional health, social support	A pilot trial of interconceptional primary medical and dental care with social support for black women with a prior VLBW birth reduced the risk of subsequent VLBW birth.
Ickovics, 2003 (144)	VPT birth ^c , VLBW ^d	Preconceptional health, social support	Group-centered prenatal care for high-risk women resulted in a nonsignificant reduction in VLBW/VPT birth risk compared with standard prenatal care in a largely black study population.
Andrews, 2006 (112)	VPT birth ^c	Inflammation	Histologic evidence of inflammation in the placenta was more common in black women than white women with VPT birth.
Goldenberg, 1998 (46)	VPT birth ^c	Inflammation	Bacterial vaginosis and fetal fibronectin were more prevalent and were stronger predictors of VPT birth for black women compared with white women.
Adams, 2000 (89)	VPT birth ^c	Life course (SES? acute, chronic, or early-life stress? genotype/epigenetics?)	Recurrent VPT birth is more common in black women than in white women.
Kistka, 2007 (88)	VPT birth ^b	Life course (SES, acute, chronic, or early-life stress? genotype/epigenetics?)	VPT birth recurrence is greater for black women than for white women.
David, 1997 (165)	VLBW ^d	Life course (acute, chronic, or early-life stress?)	Among high-SES mothers, African-born blacks had a VLBW risk equivalent to that for whites, but US-born blacks had 3.3 times the risk compared with whites.
Shen, 2008 (166, 167)	VPT birth ^c	Life course (vascular dysfunction? genotype/epigenetics?)	Black women were 2-3 times as likely as white women to have a VPT birth and PPROM or placental abruption; also found was a higher PPROM recurrence risk for black women compared with white women.
Collins, 2000 (77)	VLBW ^d	Interpersonal racism	Threefold elevated odds of VLBW were found for low-income black women reporting an experience of perceived racism during pregnancy.

Table continues

stressors could also be major life events but may have been temporally distant from the pregnancy, as in the case of adverse childhood events (physical or sexual abuse, death of a parent). Alternatively, preconceptional stressors could

be conceptualized as chronic over a significant portion of the woman's life, as would occur from long-time exposure to poverty, perceived discrimination, high-crime neighborhoods, or ongoing abuse.

Table 1. Continued

Author, Year, (Reference No.)	Outcome	Pathway ^a	Results
Collins and Lespinasse, 2004 (76 and 78)	VLBW ^d	Interpersonal racism	Among black mothers, lifetime exposure to interpersonal racism was associated with VLBW.
Aveyard, 2002 (168)	VPT birth ^f	SES	SES accounts for a large portion of the Afro-Caribbean:white, but not African:white, disparity in the United Kingdom.
Kleinman, 1987 (169)	VLBW ^d	SES	The protective effect of a higher level of maternal education was greater for white women compared with black women.
Reagan, 2005 (170)	VPT birth ^e	SES; acute, chronic, or early-life stress; substance abuse; preconceptional health	Neighborhood poverty was associated with VPT birth in black women but not white or Hispanic women; tobacco, alcohol, and cocaine use was associated with VPT birth in white women but not black women.
Geronimus, 1996 (84)	VLBW ^d	SES; acute, chronic, or early-life stress—age	For black women but not white women, increasing maternal age was associated with VLBW risk, which was stronger for low-SES than high-SES black mothers.
Rauh, 2001 (86)	VLBW ^d	SES; acute, chronic, or early-life stress—age	Increasing maternal age increases VLBW risk for black women but not white women, a pattern exaggerated among Medicaid-eligible compared with -noneligible black women.
Schempf, 2007 (85)	VPT birth ^c	SES; acute, chronic, or early-life stress—age	Older, multiparous, black women have a higher risk of VPT birth than similar white women do, and this risk is not modified by SES.
Kramer, 2008 (171)	VPT birth ^c	Social environment	Black:white disparities vary significantly across US cities independent of individual SES, explained in part by degree of residential segregation and proportion of black women living in poverty.
Khashan, 2009 (71)	VPT birth ^e	Acute, chronic, or early-life stress	Risk of VPT birth for white Danish women in the index pregnancy increased if the mother experienced death or major illness of an older child in the 6 months prior to conception of the index pregnancy. This association persisted when analyses were restricted to mothers with a prior preterm birth.
Neggers, 2006 (61)	VPT birth ^c	Acute, chronic, or early-life stress	In a predominantly black population, women below the median on a psychosocial stress scale had a nonsignificant increased risk of VPT birth compared with those above the median on the stress scale.
Sable, 2000 (62)	VLBW ^d	Acute, chronic, or early-life stress	Perceived stress and major life events were associated with increased risk of VLBW for black women and white women (not stratified on race).
Nabukera, 2009 (172)	VPT birth ^c , VLBW ^d	Acute, chronic, or early-life stress—age; preconceptional health	The black:white racial disparity in VLBW/VPT birth persists among women postponing their first pregnancy until after age 30 years. An IPI of <6 months is associated with VLBW/VPT birth in the second pregnancy.
Goldenberg, 2007 (173)	VPT birth ^c	Vascular dysfunction	Black women and white women with VPT birth had a similar prevalence of placental lesion, suggesting vasculopathy.
Yang, 2001 (174)	VPT birth ^c	Vascular dysfunction	Vaginal bleeding was associated with increased risk of VPT birth; a greater magnitude of effect was found in white women compared with black women.

Abbreviations: IPI, interpregnancy interval; PPROM, preterm premature rupture of membranes; SES, socioeconomic status; VLBW, very low birth weight; VPT, very preterm.

^a Entries in this column refer to nodes in Figure 2 that were evaluated in each study.

^b VPT birth was defined as <34 weeks' gestation.

^c VPT birth was defined as <32 weeks' gestation.

^d VLBW was defined as weight <1,500 g.

^e VPT birth was defined as <33 weeks' gestation.

^f VPT birth was defined as <28 weeks' gestation.

The most proximate mechanisms commonly used to explain the effects of maternal stress on prematurity are dysfunction of the maternal-placental-fetal hypothalamic-pituitary-adrenal axis or alteration of maternal susceptibility and immune response to infection. A broader explanation first articulated by Geronimus is termed the “weathering” hypothesis (18). This idea posits that chronic exposure to psychosocial and environmental stressors prematurely ages exposed women, shifting age-related risk to the peak of re-

productive activity. In the following paragraphs, evidence for each of these hypotheses is discussed and then applied to VPT birth.

Biologic pathways from stress to preterm birth

Hypothalamic-pituitary-adrenal dysfunction. Because the hypothalamic-pituitary-adrenal axis is so relevant in both normal physiologic responses to psychosocial stress (19) and

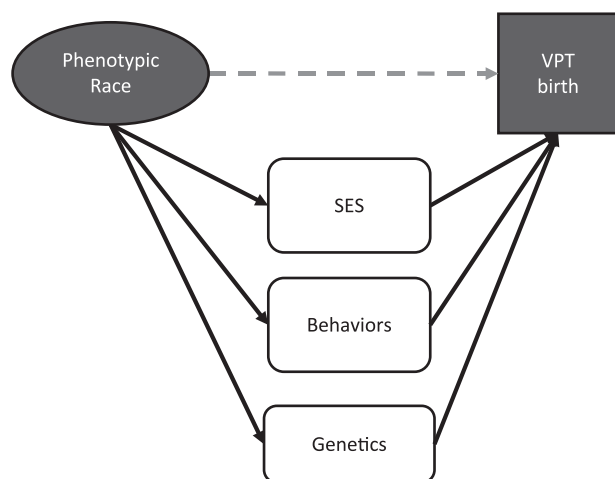


Figure 1. Traditional conceptual framework for explaining the association of race with very preterm (VPT) birth (<32 weeks' gestation). SES, socioeconomic status.

the regulation and timing of birth, this system has garnered a great deal of attention in terms of understanding preterm birth (20–22). In the normal pregnancy, both the absolute levels of placentally produced corticotropin-releasing hormone (CRH) and its rate of increase throughout pregnancy may trigger the eventual cascade resulting in cervical softening, weakening of the fetal membranes, uterine contraction, and birth (23). The question of a neuroendocrine role in premature birth is raised by the observation that measured maternal serum CRH is elevated in women who subsequently deliver prematurely (24–26). Data from prospective

cohorts note increases in both absolute CRH and the trajectory of CRH increase as early as the midsecond trimester in women who subsequently deliver preterm compared with those who deliver at term (27–29). Thus, CRH may be a marker of a “placental clock” that is set early in gestation and determines length of gestation (30–32).

Observed racial differences in maternal median CRH have been reported, but with differing findings. Herrmann et al. (33) reported an overrepresentation of black women in the “high CRH” group compared with white women. Holzman et al. (34) found differences in maternal CRH measured at 15–19 weeks' gestation in a multiracial, nested case-control study. Black women who delivered both at term and preterm had lower median CRH levels compared with white women in either group; however, within each racial group, CRH was negatively associated with length of gestation, and this association was stronger for black women than white women. Wadhwa et al. (35) also reported lower CRH and cortisol levels in black compared with white pregnant women but noted elevated adrenocorticotrophic hormone in black women at all gestational ages and a lower gradient of CRH increase across gestational ages.

Hobel et al. (36) reported that maternal perceptions of stress at 18–20 weeks' gestation explained a significant proportion of the difference in CRH at 28–30 weeks between women who subsequently delivered preterm rather than at term. Maternal stress has also been linked in pregnancy to elevated levels of several other components of the hypothalamic-pituitary-adrenal axis, including adrenocorticotrophic hormone, β -endorphin, and cortisol (37). Although some general patterns of maternal stress, elevated CRH, and spontaneous preterm birth are consistent across racial groups, differences do exist. Glynn et al. (38) reported patterns of CRH, cortisol, and adrenocorticotrophic hormone

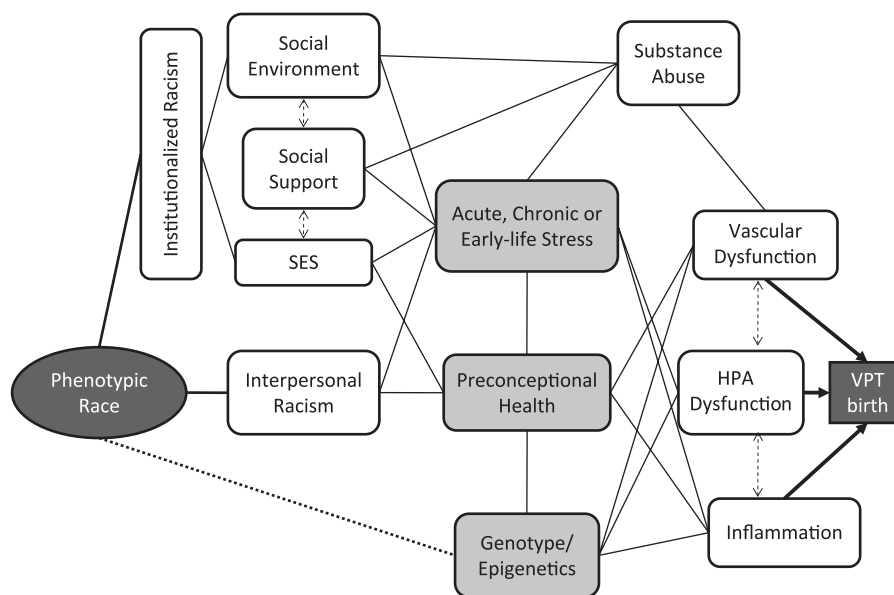


Figure 2. Alternative conceptual framework for understanding the association of race with very preterm (VPT) birth (<32 weeks' gestation). HPA, hypothalamic-pituitary-adrenal axis; SES, socioeconomic status.

for black women that are similar to the hypothalamic-pituitary-adrenal dysregulation seen in posttraumatic stress disorder and other chronic stress syndromes and are distinct from those patterns seen in acute stress responses.

Immune and vascular dysfunction. Psychosocial stress may also lead to preterm birth by altering immune system function either independently or in interaction with the neuroendocrine dysfunction (39). A review of 300 studies of the relation between psychological stress and immune response found that the impact varied depending on the chronicity of the stress (40). Acute stressors tended to up-regulate immune responses, whereas chronic stressors tended to suppress both cellular and humoral immune activity. Evidence from both pregnant and nonpregnant populations supports the connection of stress and immune status.

C-reactive protein is a general marker of inflammation that may be predictive of preterm birth (41). One study in a nonpregnant cohort found that the count of adverse life events was the strongest predictor of C-reactive protein and that black women reported approximately twice as many such experiences as white women did (42).

Bacterial vaginosis is a common vaginal infection implicated as a risk factor for VPT birth and is more prevalent in black compared with white women (43–46). In a longitudinal follow-up study of 3,614 nonpregnant women, stress was associated with both overall prevalence and incidence of bacterial vaginosis (47). When a case-crossover analysis was conducted, each point on a 5-point calculated stress scale conferred a 2-fold (95% confidence interval: 1.1, 3.6) elevated risk of bacterial vaginosis. In a smaller cross-sectional study of nonpregnant black women in New York City, the odds ratio for the effect of stress on bacterial vaginosis was 1.4 (95% confidence interval: 0.95, 2.1) (48). Culhane et al. (49) found that moderate to high levels of perceived stress conferred an independent 2.2-fold (95% confidence interval: 1.1, 4.2) increased risk of bacterial vaginosis in low-income pregnant women, but Trabert and Misra (50) found no association between hassles, anxiety, or social support and the prevalence of bacterial vaginosis in a sample of black pregnant women. Stress may also be associated with inflammatory periodontal disease, which itself has been associated with preterm birth and is more prevalent in black compared with white women (51–53).

In addition to directly impacting neuroendocrine or immune function in pregnancy, stress could also alter vascular function, resulting in altered placental blood flow or increased exposure to risk factors such as hypertension (54, 55). In a study of stress and cardiovascular reactivity during pregnancy in active-duty military women, black women had significantly greater reactivity than white women did, which was associated with higher risk of preterm birth (56). In a prospective study of maternal hostility or anomie (alienation from social norms), higher anomie and hostility were associated with increased systolic and diastolic blood pressures and increased heart rate (57). For black women, anomie was associated with medically indicated preterm delivery, and, for black women and white women, hostility was associated with spontaneous preterm birth.

Epidemiology of stress and prematurity

Stress as an exposure is a challenging construct for epidemiologic research because it is difficult to categorize and measure (58). Stress has been conceived of as anxiety trait, acutely stressful insults, or chronic and persistent hassle. Savitz and Pastore's review (59) of 20 studies of stress and preterm delivery suggested that anxiety states were not associated with preterm birth, whereas general stress was, with relative risk estimates ranging from 1.2 to 1.8. Subsequent to the Savitz and Pastore review, the 2007 Institute of Medicine report (17) on preterm birth identified 11 new studies and suggested that anxiety might be more important in terms of preterm birth for white women and that depression and posttraumatic stress disorder might be more important for black women. One study of black women reported little impact of anxiety but a significant association between intrusive thoughts and preterm birth (60), suggesting a possible role for preexisting traumatic life experiences in the perception of stress during pregnancy. A study with predominantly black participants found a non-significant increased risk of VPT birth for women with psychosocial stress scores below the median (indicating "poor psychosocial health") compared with above the median (odds ratio = 1.3, 95% confidence interval: 0.9, 2.0) (61). A population-based case-control study found that women who "almost always felt stress" during pregnancy had 60% higher odds of delivering a very low birth weight infant when compared with women reporting some or no stress (62).

Stress has also been conceptualized as exposure to adverse life events such as homelessness, death of a loved one, or being a victim of crime or physical and sexual abuse. A small study of black women found that a higher number of adverse life events in the year prior to and during pregnancy was associated with shortened gestational age (60). Two studies in racially mixed and one in all-black populations found approximately 2-fold elevated risks of preterm birth associated with number of stressful major life events (63–65), but 2 others found no such association (66, 67). Adverse childhood events, including sexual abuse, were also associated with preterm birth in 2 studies (68, 69) but not in a third (70) (as reviewed in Cammack, A, unpublished manuscript, Emory University). A Danish population-based study reported elevated risk of VPT birth for mothers who experienced the death of an older child in the 6 months preceding conception of the index pregnancy (odds ratio = 1.7, 95% confidence interval: 1.2, 2.4) (71).

Another characterization of stressful experiences is perceptions of discrimination or interpersonal racism throughout the life course or during pregnancy (72–74). A 2007 poll by the Pew Research Center found that 81% of blacks in the United States report "frequent" experiences of discrimination in at least one of the following categories: applying for a job, eating in a restaurant, renting or buying a house, or applying to a university or college, suggesting that perceptions of discrimination and racism were prevalent exposures among blacks as recently as 2007 (75).

A handful of studies have evaluated experiences of racism in relation to preterm birth. Collins et al. (76–78) reported similar findings in 2 hospital-based case-control studies

of a low-income, inner-city population. In each study—restricted to black mothers and their infants—mothers of very low birth weight infants were approximately 3 times as likely as mothers of normal birth weight infants to have experienced racial discrimination. In the CARDIA prospective cohort, Mustillo et al. (79) found that experiences of discrimination doubled the risk of self-reported preterm birth. In this study, control for experiences of discrimination reduced the black-white disparity by 50%. Dominguez et al. (80) reported a negative association for black women but not white women between maternal perceived racism and birth weight after controlling for medical risk factors and other types of stress. Finally, the authors of 2 additional prospective studies found a 40%–80% elevated risk of preterm birth associated with perceived racism or discrimination (63, 81, 82).

Although each of the above-mentioned classes of stress could be measured solely for the duration of the pregnancy, other authors propose a life-course model in which stress, resilience, and social support interact to impact reproductive health prior to conception (22, 83). Geronimus' weathering hypothesis contributes to the life-course perspective by suggesting that preconceptional exposures lead to premature aging and dysfunction in endocrine and immune function for some women. Circumstantial support for this hypothesis comes from racial and socioeconomic differences in maternal age and the risk profile for preterm birth. In general, risk of VPT birth is highest at the extremes of maternal age (<18 or >35 years of age), with the lowest risk in the mid-twenties. However, when stratified by race, the entire U-shaped curve for black women, and particularly for poor, black women, shifts to the younger ages compared with that for white women (84). This pattern has been replicated for preterm and VPT after adjusting for parity (85) and for very low birth weight, where the left shift was exacerbated for women of lower socioeconomic status (86). However, Ananth et al. (87) found no support for the weathering effect on preterm birth in an age-period-cohort analysis of births from 1975 to 1990. The observation that the risk of recurrent VPT birth is higher for black compared with white women also points to a life-course explanation, although whether it is genetic, epigenetic, or evidence of weathering is unclear (88, 89).

Distal sources of stress and prematurity

In addition to stress being mediated by individual-level characteristics (anxiety state, experience of abuse or violence), it has also been suggested that differential population patterns of stress exposure could result from distal social and economic contextual exposures (90). This pathway suggests that living in an area of higher crime, neighborhood deprivation, or concentrated poverty may increase the chronic stress experiences of all inhabitants net of other individual-level risk factors such as smoking, maternal education, and medical conditions. As an extension of the weathering hypothesis, Cerdá et al. (91) looked at the slope of the association between maternal age and birth weight in 342 Chicago, Illinois, neighborhoods. They reported significant neighborhood-level variation in this slope, with neighborhoods characterized by a negative slope (e.g., birth weights decline with increased maternal age) having a higher

proportion of black mothers and a greater poverty concentration. The association of concentrated poverty with a negative maternal age–birth weight slope persisted with control for race and other individual-level risk factors, and the age–birth weight slopes for neighborhoods without such a concentration of poverty were positive.

Whether such contextual exposures act through a stress pathway is unclear. One study utilized direct observation of neighborhoods combined with census data to characterize the social context of low-income pregnant women in terms of psychosocial stressors versus material deprivation (92). They reported notably different environments for poor white compared with poor black pregnant women, with black women more likely to live in environments with greater physical incivility and fewer amenities such as sidewalks. In evaluating the association of psychosocial stress with bacterial vaginosis, Paul et al. (93) also explored the role of neighborhood context. They found that although neighborhood socioeconomic status was associated with prevalent bacterial vaginosis in white women, it was not for black women; only the number of stressful life events was significant. On the other hand, Culhane et al. (94) reported that accounting for both individual as well as contextual stressors such as crime rate or prevalence of homelessness significantly reduced the black-white disparity in bacterial vaginosis for low-income pregnant women.

Living in neighborhoods with high levels of violent crime could also be a source of chronic stress. For example, increased rates of violent crime are associated with decreased birth weight for both black women and white women (95), and Messer et al. (96) reported similar findings for preterm birth, although the association was statistically significant for only black women. While these and other contextual exposures appear to increase the risk of poor pregnancy outcomes, evidence also exists that some neighborhood characteristics reduce the risk for black women. In a study of the effect of residential segregation on preterm birth, one type of segregation (racial clustering) was *protective* against preterm birth after controlling for degree of racial-isolation segregation (97). The authors suggested that social ties and networks resulting from an ethnic enclave effect offset some of the negative stressors of neighborhood environment. Similarly, 2 studies reported that, for poor black women, living in a relatively wealthier neighborhood is protective against preterm birth *if* that neighborhood is predominantly black; in racially mixed neighborhoods, there is no longer a protective effect of this income incongruity between individual and median neighborhood income (98, 99).

Finally, the stress pathway may interact with known risk behaviors in a way that leads to preterm birth. For example, smoking is a modest risk factor for prematurity and is generally less prevalent among black compared with white pregnant women (67, 100–103). Bell et al. (104) looked at the prevalence of smoking among black pregnant women as a function of metropolitan area residential segregation. They report a U-shaped association between segregation and smoking, concluding that, in highly segregated cities, urban stressors and targeted tobacco marketing in black neighborhoods result in increased prevalence, whereas, in cities with

the lowest amount of segregation, smoking prevalence increases because of equivalent behaviors of white women and black women. In another study, increased psychosocial stress and lower social network support was predictive of smoking, alcohol, and substance use (marijuana and “hard drugs”) for low-income pregnant black women (105). For white women, physical abuse, but not social support, was predictive of these risky pregnancy behaviors.

PRE- AND PERICONCEPTIONAL MATERNAL HEALTH

Although acute or chronic psychosocial stress is hypothesized to interact with maternal health, there is also evidence that other aspects of preconceptional and prenatal health status could transmit racially disparate pregnancy outcomes. Identifying modifiable health status indicators of preterm birth risk could allow implementation of effective interventions through delivery of health services such as primary care, prenatal care, family planning services, and health education.

Preconceptional health

Many facets of a woman’s health prior to conception could possibly influence the probability of carrying the pregnancy to term (106). Data from 26 states’ Pregnancy Risk Assessment Monitoring Systems suggest that, prior to conception of an index pregnancy, black women are more likely than white women to have prevalent diabetes, hypertension, and anemia and are less likely to be taking multivitamins or to have had prepregnancy health counseling or recent dental care (107). The following paragraphs review evidence for the role of systemic inflammation, altered vascular function, and general access to well-woman health care.

Infection and inflammation. Maternal genital tract infection and the resulting host inflammatory response are associated with as many as 30%–70% of preterm births, with an inverse association between prevalence of culture-positive amniotic fluid and gestational age (108–111). Culture-confirmed infection is not only highly prevalent in VPT birth but also more common among VPT births to black women compared with white women (46, 112). Although genital tract infections such as bacterial vaginosis are presumably the leading culprit (113), growing evidence for an association between periodontal gum disease and VPT birth suggests that host inflammatory response distinct from a site-specific infectious organism may be relevant (53, 114).

Attempts to reduce preterm birth risk by treating prevalent genital tract or dental disease during pregnancy have proved disappointingly ineffective (115, 116). What remains unclear is whether preconceptional treatment of such infections would reduce subsequent pregnancy risk. One trial of interconceptional antibiotic treatment for women with a prior preterm birth failed to demonstrate reduced risk in the subsequent pregnancy (117, 118). Some evidence exists that prenatal treatment of severe periodontal disease reduces subsequent risk of preterm birth (119), and one pilot trial of interconceptional care (including primary care and dental treatment) for women with a prior very low birth

weight infant showed a reduced risk of subsequent very low birth weight delivery for black women (120).

Chronic disease. The observation that women who deliver an infant preterm have a subsequently increased risk of cardiovascular disease suggests linkage between pregnancy outcome and life-course chronic disease (121, 122). Preexisting maternal hypertension or diabetes mellitus can lead to placental insufficiency, heightened risk of preeclampsia, and indicated preterm birth. The rising population prevalence of hypertension and type 2 diabetes at younger and younger ages may make these causes more important in pregnancy outcomes. Chronic and gestational diabetes increase the risk of preterm birth by 30%–90%, and chronic hypertension can increase the risk approximately 2-fold (123–125). Even though the magnitude of the effect is similar between races, the preconceptional prevalence of both diabetes and hypertension is higher among black women than white women (107, 125). However, population studies do not show an appreciably diminished magnitude of the racial disparity in VPT birth after control for preconceptional health status (102, 123).

Grady and Ramirez (126) attempted to estimate the role of preconceptional chronic disease as a mediating factor between distal social exposures and subsequent low birth weight. They concluded that, for black women, some of the association between neighborhood residential segregation in New York City and low birth weight is mediated by the increased prevalence of chronic and pregnancy-related hypertension among women in those neighborhoods.

Well-woman care. Perhaps one of the biggest challenges for the traditional approach to pregnancy care is the notion that pregnancy is not an isolated island of health or lack of health, but rather a period integrally connected to the life-course health of women (and men) (127). Factors that may be relevant to this life-course perspective include access to primary health care and issues of family planning, including pregnancy intention and interpregnancy interval.

Having health insurance is associated with use of effective contraception and preconceptional use of multivitamins, but adequate coverage outside of pregnancy is unavailable to many, particularly low-income women of color (128–130). Pregnancy intention is closely linked to access to and use of effective contraception (131), and conceiving an unintended or unwanted pregnancy is associated with preterm delivery (132–134). The length of the interpregnancy interval is also tied to effective access to primary health care service, and it appears to be strongly related to the occurrence of VPT birth, with shortened intervals of less than 6 months doubling the risk compared with an ideal interval of 18–23 months (135–137). Finally, in one study, users of preconceptional multivitamins appeared to be at lower risk of VPT birth, and black women were half as likely to use multivitamins (138).

While there are racial differences in access to primary health services, there is also evidence that perceived racial discrimination in seeking health care is associated with poor self-reported health for black adults, irrespective of health insurance status (139). Whether this finding is relevant for reproductive health specifically is unknown.

Prenatal health

Intuitively, pregnancy complications could best be prevented by application of pregnancy-related health care. Unfortunately, prenatal care is notable for its lack of expected effect on preterm birth. Early observational research found a protective effect of adequate prenatal care on the risk of preterm birth and low birth weight (140, 141). These results were likely a product of selection bias because women at low risk of preterm birth are also high users of prenatal care. A randomized trial of aggressive prenatal education and care for high-risk women found no difference in preterm birth risk between the intervention and control groups, nor any appreciable difference between study participants (who all received care) and population estimates for preterm birth (142). Similarly, a population-based study limited to participants who all entered prenatal care in the first trimester reported rates and disparities of preterm birth and perinatal mortality similar to those for nonrestricted populations (143). Whether specialized, risk-targeted prenatal care will prove more useful remains to be shown, although some models are promising (144, 145).

GENETIC AND EPIGENETIC PATHWAYS TO PREMATURITY

The body of literature that mentions genetics as an explanation for the racial disparity in preterm birth is large, but notable for rarely measuring genes; most studies suggest that residual racial variation in preterm birth risk is genetic after statistical control for measured socioeconomic and behavioral risk factors. This could be problematic because of the persistence of residual socioeconomic confounding in even the richest of data sets commonly available for epidemiologic research (146), as well as the complex causal web suggested by Figure 2. Only relatively recently have specific hypotheses of variation in measured genetic and epigenetic (e.g., variation in gene expression in the absence of varying DNA sequence) traits been proposed and tested. While these early studies are promising, they suffer from the same problems of multiple testing, reproducibility, sample size, and general “needle-in-a-haystack” phenomena seen in other areas of genetic research in a post-Human Genome Project era (147).

The utility of considering genetics at all in understanding racial disparities in health is being vigorously debated (refer to Ioannidis et al. (148), Kaufman and Cooper (149), and Frank (150) for further discussion). However, there are 3 scenarios in which genetic research could be helpful in understanding the racial disparity in prematurity: 1) identification of genetic polymorphisms that are causally linked to risk of preterm birth and are differentially prevalent among black women and white women; 2) identification of genetic polymorphisms that are equally prevalent by race but that interact with social or environmental exposures that are differentially prevalent by race; or 3) identification of social or environmental exposures that are differentially prevalent by race and that alter normal genetic expression, resulting in an epigenetic racial variation in protein synthesis or function. Of the small body of literature seeking specific genetic

mechanisms responsible for preterm birth, most assume that the first scenario is true, although arguably the second and third offer the most opportunity for intervention.

In one of the largest-scale candidate gene studies to date, Velez et al. (151) evaluated the association between 1,432 single nucleotide polymorphisms in 130 candidate genes from the inflammatory, vascular, and neuroendocrine pathways and related them to gestational age for pregnant black women. Their findings are consistent with some previous literature, in that the strongest associations between genotype and the phenotype of preterm birth were in the infection and inflammation pathway. The most commonly studied genes in this pathway are those regulating interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha. Findings regarding racial differences in prevalence of candidate gene polymorphisms vary, even for the same polymorphism, with a few reports of difference for tumor necrosis factor (152–154) and interleukin-6 genes (152, 155). In only one of these studies (155) is the observed racial difference in polymorphism prevalence explanatory of preterm case-control status ($P = 0.04$), an association not corrected for multiple comparisons. Simhan et al. (156) found that a polymorphism of the interleukin-6 promoter region was protective against VPT birth for white women but was completely absent in the 58 black women cases or controls in the study.

Studies that jointly consider genetic polymorphisms and the presence of bacterial vaginosis suggest that gene-environment interactions may be important. Macones et al. (157) reported a similar prevalence of tumor necrosis factor alleles in blacks and whites but noted (for both blacks and whites) a 6-fold elevated risk of preterm delivery for carriers of the rarer variant who also had bacterial vaginosis. Similar interactions were reported for tumor necrosis factor (153, 158, 159) and interleukin-1 (158, 160). A single report of an interaction between maternal smoking and a mitochondrial DNA variant suggests that other gene-environment interactions may be worth examining as well (161). Fortunato et al. (162) reported different racial patterns of gene-gene interactions between tumor necrosis factor-alpha and interleukin-6 genes in relation to preterm birth but did not evaluate whether these different patterns account for any of the disparity.

While promising, genetic studies to date have been limited by small sample sizes and the near absence of research on births of <32 weeks' gestation compared with <37 weeks' gestation. If VPT births are at all etiologically distinct from the more common late-preterm births, this exclusion could mean a heterogeneous mix in the case population, reducing power to identify important pathways.

DISCUSSION

Simple approaches have thus far failed to explain the long-standing problem of racial disparities in prematurity. Evidence that the biologic pathways, maternal risk profiles, and magnitude of the racial disparity all vary between extreme and moderate categories of prematurity means that pooling all preterm births obscures patterns that may be informative. Wilcox (8) notes that a birth weight of

<1,500 g (an outcome highly correlated with VPT birth) is a crude measure of the size of the residual distribution of births composed of truly high-risk infants, emphasizing again the etiologic and epidemiologic distinction between extreme and moderate outcomes.

We found growing evidence to support the role of socially patterned maternal stress, possibly over the life course, as a cause of racial disparities in VPT birth. We also found evidence for racial differences in the propensity for a pregnant woman to deliver prematurely because of host inflammatory response or vascular and neuroendocrine dysfunction. What is largely missing in the literature, with a few exceptions, are studies that informatively combine these 2 patterns in ways that increase our understanding and illuminate opportunities for effective intervention. Figure 2 is an attempt to depict how these patterns could be studied, although it just begins to represent the complex causal pathways that may link the social construct of race to the serious biologic outcome of VPT birth. Future studies should incorporate a rich causal framework while attending to outcome specificity, study design, and data sources.

When possible, a broader selection of potential factors should be incorporated into the study design. For example, social and environmental factors that are measured precisely with established instruments should be included routinely in studies primarily focused on finding genetic differences. Likewise, hypothesized biologic markers should be routinely incorporated into all preterm birth studies of racial disparities.

Epidemiologists have long critiqued the overuse of readily available, large-scale vital statistics data sets. It is clear that vital statistics data sets have many limitations in terms of testing hypotheses, even when they appear to have a variable that closely proxies the exposure or outcome of interest. Nonetheless, for questions of racial disparities in a relatively rare outcome, the benefits are undeniable. Understanding geographic variation, racial differences in maternal age-related risk, and differences in mortality by gestational age would be cost prohibitive without use of vital statistics.

However, if researchers are to explore the more complicated linkages between race and VPT birth suggested by Figure 2, new approaches will be needed. Creative ways to combine vital statistics (e.g., maternally linked or inter-generationally linked birth records) with richer clinical and social information, or approaches that identify cohorts of prepregnant women and follows them for risk, may allow exploration of some of the life-course questions raised.

Clearly, one of the biggest challenges in addressing the racial disparity in VPT birth is our incomplete understanding of what the causal web looks like. Whereas, on some level, all disease may boil down to a combination of genes, environment, and individual behaviors, understanding the reason for population differences in health requires more sophistication, or at least a very broad view of how each of these interact. At a minimum, researchers should articulate the causal thinking that underlies their research, including identifying the section(s) of the causal network represented in their work and addressing how the missing section(s) limits their results. Eventually, results from these studies that individually answer only a small part of the

puzzle may be pieced together to form a coherent explanation that will lead to meaningful interventions and elimination of the racial disparity in VPT birth.

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