



Stress model for research into preterm delivery among black women

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KEY WORDS

Preterm delivery
Stress
Black race
Racism

The disparity between black and white infant mortality rates increased over the last decade, despite overall improvement in infant survival. Because most black infant deaths are related to preterm delivery, the discovery of the cause of premature birth in general and excess premature birth for black infants in particular is of paramount importance for reproductive health research. Substantial theoretic support exists for maternal stress as a risk factor for preterm birth. Traumatic events early in life may sensitize the adult to contemporary stresses and increase her vulnerability to stress-induced neuroendocrine or infection/inflammatory pathways to early parturition. In addition, an individual may prematurely age as a result of cumulative stress or a major traumatic event. This “stress age,” which is synonymous with the concept of weathering and similar to the concept of allostatic load, may affect parturition through chronic conditions (such as hypertension) and in poorly understood pathophysiologic mechanisms that are related to increased chronologic age. One potential measure of stress age is maternal serum dehydroepiandrosterone sulfate. Maternal stress is a potential explanatory factor for excess preterm delivery among black women because of their exposure to racism-associated stress. However, few studies have addressed this question, and results are mixed. Future etiologic research must take into account the complexities of the measurement of stress age and past and current exposures to stress, which includes internalized racism and interpersonal racism.

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Infant mortality rates in the United States reveal a wide and growing racial gap. In 2001, the infant mortality rate per 1000 live births was 5.7 for infants of white mothers, but 13.3 for infants of black mothers; this is a 2.3-fold excess death rate.¹ During recent years, infant mortality rates have dropped for all racial and ethnic groups, but the decrease has been paradoxically more dramatic for groups with lower initial rates. Between 1995 and 2001, there was a 9.5% improvement

for non-Hispanic white infants, but only an 8.2% improvement for non-Hispanic black infants.¹

Preterm delivery accounts for a large portion of the excess mortality rate among black infants. Whereas 2 decades ago, black infants who were born preterm or of low birth weight were more likely to survive than white infants of the same gestational age or birth weight,² in 2001 black infants were less likely to survive, regardless of gestational age or birth weight category.¹ By applying the birth weight and gestation distributions of white infants and their birth weight– and gestation-specific infant mortality rates to black infants, we found that three-fourths of all excess deaths of black infants were

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among those who weighed <1500g or with gestational age of <32 weeks. Further, for those infants, almost 80% of the excess deaths were attributable to their size or gestation, not to their slightly higher mortality rate. Thus, the determination of the causes for higher preterm delivery among black infants is a crucially important step towards the development of interventions to reduce their risk.

Maternal stress as a potential cause of excess black infant mortality rates

A clue to the cause of excess black infant death may be found in the strikingly high excess mortality rate among infants who are born to college-educated parents. Since first reported for the cohort of infants who were born in 1980,² a consistent finding is that, compared with college-educated white parents, black college graduates are much more likely to experience an infant loss. For infants who were born during the 1983 to 1985 period, the crude odds ratio was 1.9. Adjustment for early prenatal care, parity, maternal age, and marital status only accounted for 10% of the excess (adjusted odds ratio, 1.8).³ Despite the fact that many well-educated black women obtain prenatal care beginning in the first trimester, the relative risk of death among their offspring has increased over time, amounting to a 2.9-fold excess among infants who were born in 2001.¹ Most of the differential mortality rate is owing to excess risk of preterm and very low birth weight deliveries.

One hypothesis for this dramatic differential is that, compared with white women, black women experience higher lifetime exposure to chronic and acute stressors, which includes stressors that are associated with racism, that increase their risk of stress-associated pregnancy complications, which include preterm delivery. Although stress is not established as a pregnancy risk factor, the stress hypothesis has biologic plausibility⁴ and currently is being investigated in several epidemiologic studies of prematurity.⁵⁻⁸ Because of the unexplained risk of preterm delivery among well-educated black women, their exposure to the stress of racism has been posited as a risk factor that may set them apart from similarly educated white women.⁹⁻¹¹ We view the individual's exposure to racism in its various forms as a type of chronic stress. For well-educated black women, the stress of living with race-associated income differentials, coupled with coping with interpersonal racism experienced throughout their lifetime may age them prematurely and make them and their fetuses more vulnerable to stress-associated pregnancy complications.

In general, stress is complicated to measure, is multifaceted, and includes acute experiences and accumulated effects of lifetime exposures to hassles, deprivation, and crises.¹²⁻¹⁵ We know from studies of individuals with major depression¹¹⁻¹³ or posttraumatic stress disorder¹⁶⁻¹⁸

that major acute events in the past may continue to be experienced as stress in the present and may affect how other stressors are experienced. For example, a study of Vietnam veterans showed that experience of childhood abuse was associated with a 4-fold increased risk for the development of posttraumatic stress disorder from Vietnam combat, after being controlled for a number of factors.¹⁹ This association was found even among men without psychiatric disorder before they went to Vietnam. Such an excess risk from early childhood trauma is known as stress sensitization, which can be modeled in animals.

With respect to reproductive health, various investigators have modeled how maternal stress may affect immune, endocrine, and vascular functioning, which in turn affect uteroplacental function and eventually increase the risk of preterm delivery.²⁰⁻²² For example, Wadwha et al²⁰ posit 2 physiologic pathways whereby maternal stress may increase prematurity risk: (1) a neuroendocrine pathway of hyperactivation of the maternal-placental-fetal endocrine systems that are involved in parturition and (2) an immune/inflammatory pathway in which both systemic and local (placental-decidual) maternal immunity may be modulated through maternal stress to increase susceptibility to intrauterine and fetal infectious-inflammatory processes. Activation of inflammatory processes would, in turn, promote parturition through proinflammatory mechanisms. Placental corticotrophin-releasing hormone may serve to orchestrate both the neuroendocrine and the immune/inflammatory pathways.

Because the processes in these pathways cross-regulate each other, Wadwha et al²⁰ postulate an interaction and multiplicative effect on preterm delivery of chronic stress and infectious pathogens in pregnancy. If such an interaction exists, it may help to explain the higher preterm delivery rate among black women who are already stressed, for example, by poverty^{23,24} or dysfunctional family situations^{23,25} or a history of child abuse.²⁶ These and other known risk factors do not account entirely for racial disparities in sexually transmitted diseases,^{25,27,28} which suggests that, regardless of socioeconomic status, black women may be at greater risk of any stress/infection interaction that may exacerbate the risk of preterm delivery. The explanation for this excess risk so far has eluded investigators. It may be rooted, in part, to the inadequate measurement of race-associated stress and, perhaps also, an inadequate assessment of sexually transmitted disease prevalence among more affluent and well-educated women.

Wadwha et al²⁰ also postulated that characteristics of maternal stress (ie, its nature, duration, and timing) may affect the impact of stress on neuroendocrine and infection/inflammatory processes. We would agree and further hypothesize that, because of a woman's early life events and preconception, chronic stresses may age her

prematurely and thereby affect her risk of preterm delivery through other biologic processes that mimic chronologic ageing.

In addition to this stress ageing, ongoing stressors during the time of pregnancy may contribute to preterm delivery. Corticotropin-releasing factor is a stress-sensitive peptide that is released from the hypothalamus, which causes the release of adrenocorticotropin hormone from the pituitary, which in turn causes the release of cortisol from the adrenal gland. Corticotropin-releasing factor is present in both the maternal and placental circulation. Stress-induced elevations in corticotropin-releasing factor may contribute to preterm delivery, an effect that is thought to be mediated by the stimulation of cortisol production from the adrenal gland of the fetus.²⁹ Stress could also lead to preterm delivery through disruption of the reproductive hormonal system. Gonadotropin-releasing hormone is normally released in a pulsatile fashion from the hypothalamus, to cause the release of luteinizing hormone and follicle-stimulating hormone from the pituitary, which in turn results in the release of estradiol from the ovaries. Stress results in a disruption of the pulsatility of gonadotropin-releasing hormone, with associated changes in sex hormones, which includes estradiol.^{30,31} These changes in the hormonal milieu could also contribute to a premature initiation of labor and preterm delivery.

Stress age

An individual may age prematurely because of her exposure to traumatic events early in life and her continual over-exposure to life's difficulties that result from poverty or a particularly large number of stressful life events. When the individual's ability to handle acute and chronic stress or even the "natural" stress of pregnancy is overwhelmed, the impact is felt as premature ageing. We term this premature aging process stress age, to contrast it with chronologic age. Stress age is synonymous with Geronimus' concept of weathering, which she has found to be associated with adverse pregnancy outcomes and hypertension among black and poor women.³³⁻³⁵ Stress age parallels McEwen's³⁶ concept of allostatic load, "the cumulative wear and tear that the body experiences as a result of daily life experiences, differences in individual life style, major life events, and socioeconomic status," although attempts to measure allostatic load have at times mixed together measures of ageing and measures of the impact of ageing on metabolic processes.³⁷ Although stress ageing is not limited to black women, we hypothesize that the ongoing racism that most black women experience throughout their lifetime increases the rate of stress ageing among black women and includes well-educated black women of childbearing age.

Stress age is hypothesized to increase health risks in much the same way that chronologic age increases maternal risk. It may operate through a variety of physical pathways that include, but are not limited to, possibly increasing the woman's sensitization to stress and vulnerability to acute infectious agents, which might operate through the neuroendocrine and infection/inflammatory pathways discussed earlier. Stress age may increase the risk of chronic hypertension, pregnancy-induced hypertension, type 2 diabetes mellitus, gestational diabetes mellitus, central adiposity, and other manifestations of the metabolic syndrome.³⁸ Although racism-associated stress has not been examined with respect to the effects of stress age on pregnancy outcome, one aspect of racism-associated stress (ie, internalized racism) has been found to increase the risk of obesity, central adiposity, and hypertension among black-Caribbean women in Barbados.^{39,40}

To date, there is no standard method to measure stress age (as distinct from chronologic age). There may be differences in the various stressed populations that have been studied. For example, stressed individuals with depression may not have the same neuroendocrine profile as individuals who experience chronic work stress who do not meet criteria for a psychiatric disorder.³⁷ Because of the relationship between chronologic age and decreasing dehydroepiandrosterone concentrations⁴¹⁻⁴³ and increased cortisol with stress, some authors have hypothesized that an increased cortisol/dehydroepiandrosterone and cortisol/dehydroepiandrosterone sulfate ratio could be used as a marker of stress age.⁴⁴⁻⁴⁷ An association between higher cord levels of dehydroepiandrosterone sulfate and higher birth weight and longer gestational age have been reported.⁴⁸ In this study of 86 normal singleton deliveries, maternal serum dehydroepiandrosterone sulfate was associated negatively with maternal chronologic age, but this study did not measure maternal stress or stress age. The 50 white and 34 black women had similar levels of maternal dehydroepiandrosterone and dehydroepiandrosterone sulfate and their offspring had similar cord levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate; however, there was no control for birth weight, gestational age, or maternal age in the cross-racial comparison.

Stress age may depend, in part, on the individual's genetic resistance to stressors.^{13,49-51} Possible candidate polymorphisms are the neurotransmitter-metabolizing enzyme monoamine oxidase A, which has been found to moderate the effect of child abuse among men,⁵² and a functional polymorphism in the promoter region of the serotonin transport (5-HTT) gene, that has been found to moderate the influence of stressful life events on depression.⁵² There is also an age-dependent accumulation of mutations in human mitochondrial DNA.⁵³ It is conceivable that individuals of the same

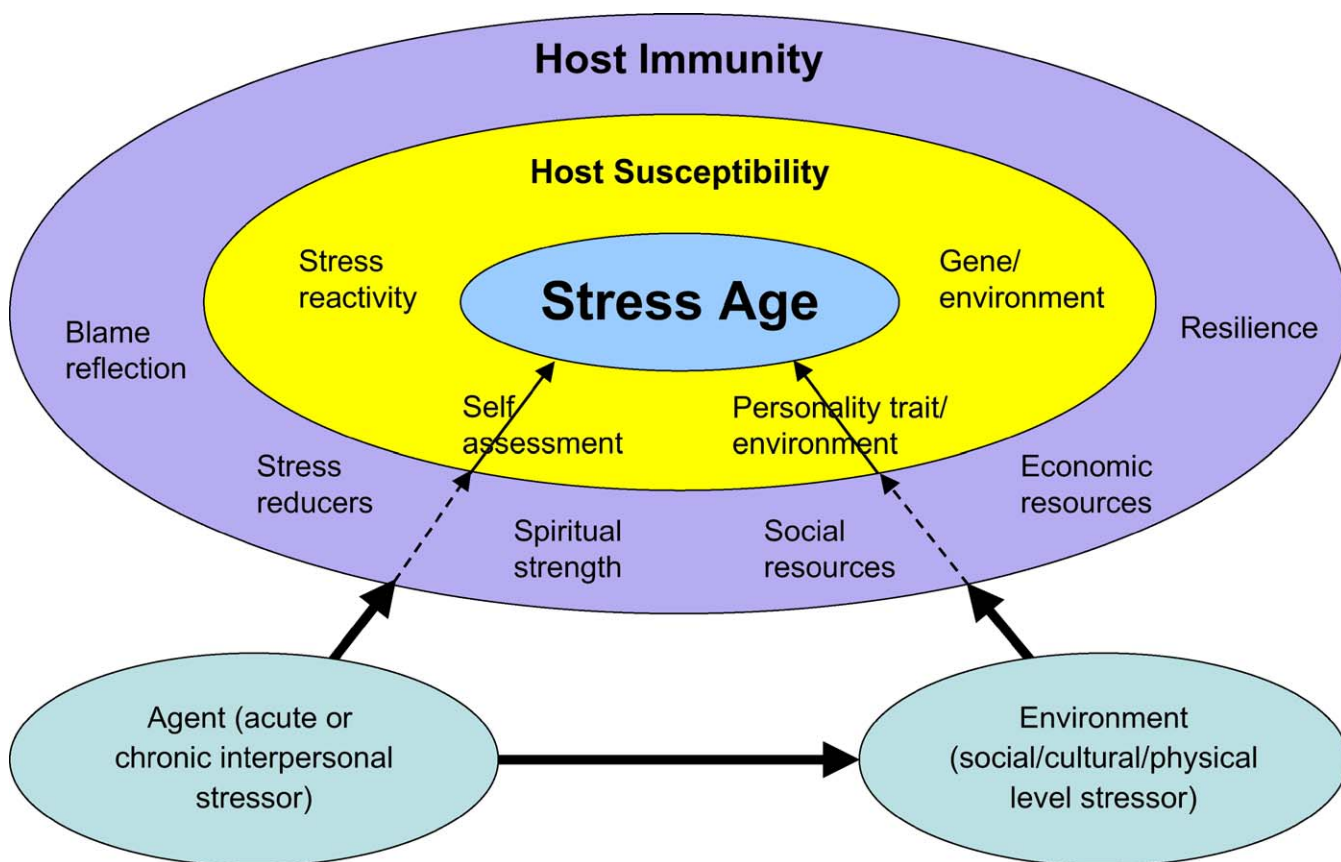


Figure Hypothesized effect of stress on stress-aging, with the use of the agent/host/environment model.

chronologic age, but differing stress age, would show differences in the accumulation of mitochondrial mutations.

Agent/host/environment model

Racism is a particular stress that is experienced by persons of color in this country, which may be additive to the overall experience of daily hassles and acute events.^{54,55} Alternatively, racism-associated stress may increase the overall impact of other stresses as well, through its impact on perception, coping responses, and psychological and physiologic stress responses.⁵⁶ We focus on the potential health impact of racism through the epidemiologic lens of the agent, host, and environmental model of disease causation (Figure). This model relates racism as both a direct stressor and an indirect environmental stressor to the individual’s host susceptibility to stress.^{13,49} We have refined a model that was originally introduced in a discussion of black women’s health disparities³⁵ to illustrate the potential impact of racism as an acute and chronic stressor that operates to increase stress age on the risk of preterm delivery. As the Figure indicates, any investigation of the racism/preterm

delivery pathway should include a measurement of mediators, moderators, and indicators of stress age. Selected measures for each component in the model are provided as suggestions for inclusion in future research in this area.

Black women are exposed to stress from early life experiences, stressful life experiences, and daily hassles. Some stress is gender and race related.⁵⁷ Jackson et al^{32,57} have developed and tested a race- and gender-specific stress measure through a multidisciplinary process that used qualitative and quantitative methods. Initiated by a grounded theory approach, the process and the subsequent measure sought to capture the authentic experiences of stress and support among black women.

Based on this research, Hogue⁴⁹ developed an epidemiologic theory of the impact of these stresses on the individual’s immunity to stress-associated illness. This model posits that the added stress of dealing with interpersonal and institutional racism increases the host’s susceptibility to stress-associated diseases, to the extent that the host’s ability to withstand stress is compromised. Factors that are associated with “host immunity” to stress include blame reflection, active coping strategies that reduce stress (including physical

activity), spiritual strength, social resources, economic resources, and resilience. Factors that increase “host susceptibility” include heightened stress reactivity (which may be associated with early life stressors) and internalized racism (which may be associated with previous race-related stressors), personality traits of higher anger and anxiety traits and anger expression that is either held in or over-expressed, and active coping strategies that increase disease risk (including smoking and alcohol consumption).

The model also posits gene-environment interactions, which may occur even when there is no difference between races in the distribution of genetic polymorphisms.⁵⁸ For example, assume that group A and group B have the same distribution of a stress-susceptibility gene (such as the short form of 5-HTT, the allele for the serotonin transporter), which has been found to increase the risk of depression and suicide after exposure to stress.⁵² If group A is more exposed to stress than group B, then the rates of depression and suicide may be greater in group A, despite their similar genetic composition, because of the gene-environment interaction.

Although genetic differences are much greater within races than between them, there also may be race-associated polymorphisms that increase the risk of stress-associated disease. For example, in a search for a genetic basis for the association between the impaired corticotrophin-releasing hormone (CRH) response to stress in patients with rheumatoid arthritis, Baerwald et al⁵⁹ found that the distribution of alleles A1 and A2 and the biallelic frequencies of A1B1, A2B1, and A2B2 in the 5' region differed for white and black populations. The compound allele A1B1 was the most prevalent in English white patients (87%) but was found in less than one third of the black populations studied from South Africa (29%), Gambia (28%), and Cameroon (27%). In a later case-control investigation, the compound allele A1B1 was found to be a risk factor for rheumatoid arthritis in black South African patients.⁶⁰ The A2B1 allele was rare in the English white population that was studied (8%); however, it was the most prevalent compound allele in black populations (44% in South Africa, 61% in Gambia, and 52% in Cameroon), and was found to be protective of rheumatoid arthritis in the English population.⁶⁰

The significance of these genetic differences for preterm delivery is unknown. Although placental CRH production has been associated with the length of gestation,⁶¹ its expression appears to be regulated differently to CRH that is produced by the hypothalamus.⁶² For example, both glucocorticoids and progesterone inhibit CRH promoter activity in the hypothalamus but inhibit its activity in the placenta, which produces much more CRH during pregnancy than does the hypothalamus.⁶²

Racism as agent

The racism “agent” in this model operates in individual insults or discriminatory acts (what Jones⁶³ terms *personally mediated racism*) directly on the host (agent→host). To date, epidemiologic studies of personally mediated racism have focused primarily on the effects of racism on mental health or self-reported health status.⁶⁴ For their critical review of population-based studies of personally mediated racism, Williams et al⁶⁴ found 53 cases that met their review criteria. In general, all studies were either positive or neutral for an association (ie, no effect); none of the studies found a protective association. Mental health was the most studied outcome; of 25 studies of psychologic distress, 80% reported a significantly elevated risk for perceived racism. Only 2 of the 53 studies focused on pregnancy outcome (ie, very low birth weight). One study was a small, hospital-based case-control study of low-income, black women in Chicago.⁶⁵ The cases were women with a very low birth weight (<1500 g) infant (n = 25) and control subjects who had been delivered of an infant who weighed ≥2500 g who was admitted to a neonatal intensive care unit for ventilator management or whose infant was healthy. Control subjects with severely ill infants were included to examine the possibility of recall bias, because it was assumed that their infants' health problems were not associated with maternal prenatal stress. Because the mothers of healthy and ill control infants responded similarly with respect to racial discrimination, they were considered as one control group in the analysis (n = 60). Women were asked about their perceptions of exposure to racial discrimination during the pregnancy while at school, receiving medical care, getting service at a restaurant or store, getting housing, and at work. Having experienced racism was defined as a “yes” on at least one question. The crude odds ratio of very low birth weight for experienced racism was 1.9 (95% CI, 0.5, 6.6). In a logistic model that controlled for maternal age, parity, prenatal care, social support, smoking, alcohol consumption, and drug usage, the adjusted odds ratio was 3.3 (95% CI, 0.9, 11.3). Although this study is small and retrospective, with a relatively weak and incomplete measure of racism, the results suggest that active discrimination is a risk factor for very low birth weight among high-risk black women.

The other study of birth weight was a prospective investigation of 147 black women who obtained prenatal care in a northern California health maintenance organization of an original sample of 165 women who were interviewed during pregnancy.⁶⁶ In addition to the Perceptions of Racism Scale,^{67,68} the investigators included measures of daily hassles⁶⁹ and self-esteem.⁷⁰ Although experienced racism and low self-esteem were separately associated with higher stress, none of the 3 psychosocial variables were statistically associated with

birth weight, after being controlled for income. A major limitation of this study is that the authors did not examine for possible interactive effects of racism and higher income on birth weight, despite their finding that higher racism scores were associated with being married, being older, and having a higher educational level.

After the review by Williams et al⁶⁴ was completed, 2 additional studies have been published, with mixed results. Rosenberg et al⁷¹ reported on pregnancies among the cohort of women who participated in the Black Women's Health Study who were queried about experiences of racism in 1997. Most women (55%) reported unfair treatment on the job, followed by housing (31%) and police interaction (24%). One in 5 of the women (21%) reported that they constantly think about their race, and only 13% of the women reported never thinking about it. The women were followed for 2 years to determine subsequent pregnancy outcomes. There were 422 preterm deliveries among the 4966 deliveries. There was no overall association between the report of previous racist experience and the risk of preterm delivery. However, education-specific results suggest that compounded stresses may increase the risk. For example, among women with ≤ 12 years of education, the preterm delivery odds ratio for unfair housing treatment was 2.4 (95% CI, 1.2, 4.6). Among women with ≥ 16 years of education, the preterm delivery odds ratio for job-related, unfair treatment was 1.6 (95% CI, 1.1, 2.1). Similarly, in a prospective study of 1962 women (approximately one third of whom were black) in North Carolina, Dole et al⁷² reported that more perceived racial discrimination was associated with an elevated odds ratio of 1.4 (95% CI, 1.0, 1.9).

Mediators and moderators

The agent/host/environment model illustrated in the Figure can be used to display any individual or community-level stress as an agent. Racism is used for illustrative purposes and also because it is hypothesized to explain a meaningful amount of the excess reproductive health risks of women of color in the United States. In the host portion of the Figure, the outside shaded area contains individual mediators that serve to "immunize" or protect the individual from the effects of interpersonal and institutional stresses, including racism. These include blame reflection (ie, attributing the racism to external rather than internal causes, which has been found to be associated with increased survival among black women⁷³), stress reducers (such as physical activity and meditation), spiritual strength, social resources, economic resources, and resilience. Whatever stresses manage to penetrate the host's immunity are moderated by individual factors that may increase the individual's susceptibility to racist stresses. These include internalized racism, stress reactivity, health-

hampering behavioral coping strategies (such as smoking and risky sexual behaviors), personality traits (such as state anxiety and anger), and gene-environment interactions.

To study the impact of stress in general and the stress of racism in particular, it is important to measure and statistically control for these mediating and moderating factors. Without careful attention to the theoretic complexity of stress as a risk factor, misclassification error is inevitable. Although validated measures for each of these factors have been developed for some populations (eg, the Nadanolinization Scale for internalized racism,⁷⁴ a measure for blame reflection,⁷³ an early life events scale,⁷⁵ a depression inventory,⁷⁶⁻⁷⁸ and scales for anxiety and anger states^{79,80}), it will be necessary to determine their applicability to the particular population under investigation.^{32,57,73}

Recommendations for research

Given the limited literature to date, it is too early to determine whether interpersonal racism is a risk factor for preterm delivery among black women. However, although definitive studies are critically important, it is not too early to apply the lessons that are suggested by the current body of literature. Clinical trials are needed to pilot test methods to increase host immunity to stress through a variety of approaches (such as interdisciplinary studies of spiritual and meditation interventions, targeted blame reflection, increased physical activity, and decreased social isolation). Preliminary indications suggest that stress reduction improves the health of hypertensive individuals of black descent.⁸¹ Investigations of these approaches might prove useful for pregnant black women. To establish adequate power to detect true improvement in pregnancy outcome, intervention studies must target women with an identified need for support, rather than applying support to women, regardless of identified need.¹³

Etiologic research into the stress/racism hypothesis should take other stresses into account and control for host resistance to stress and measure internalized racism, stress reactivity, and other potential mediators and moderators of the impact of interpersonal stress on health outcomes. As a starting point, studies should use refined measures of discrimination and personality that adjust for a tendency either to deny or to embellish reports of interpersonal racism.⁸² These studies should test for the risk of preterm delivery among black women with differing levels of reported discrimination (controlling for socioeconomic status) and measures of acute and chronic stressors that are associated with poverty. Internalized racism measures and clinical tests for stress reactivity and personality traits (such as anxiety and anger expression) should be included. Investigators should include intermediate health factors (including

immunologic status, sexually transmitted diseases and other infectious diseases, blood pressure variability, and visceral adiposity). Explicit measures of stress age should be incorporated, along with justification for the particular tests that are used in the studies. Genetic markers along neuroendocrine, infection/inflammatory, and metabolic processes also should be incorporated. With such a set of comprehensive instruments, the true picture of the impact of stress, racism-associated stress, and the potential impact on excess preterm delivery among black women should begin to emerge.

Comment

In the United States every year, among the nearly 600,000 black infants who are born, more than 18,000 infants weigh <1500 g, and almost 5000 of these babies will die before their first birthday. If the distribution of black birth weight and birth weight-specific infant deaths were equal to those for non-Hispanic white infants in the United States, there would be at least 3000 fewer deaths to infants who are <1500 g at birth and approximately 4500 fewer black infant deaths, irrespective of birth weight. Although quality prenatal care is a goal for all pregnant women, it cannot solve the on-going excess infant mortality rates among black infants.⁸³ New insights are needed to understand both the overall causes of preterm delivery and the causes of excess preterm delivery among black women. The stress hypothesis offers a promising avenue for research. A theoretic basis exists for maternal stress to trigger early parturition through neuroendocrine and infection/inflammatory pathways. There is also a growing theoretic framework for an effect of early trauma or major life events to prematurely age the individual, thereby affecting other biologic processes that are necessary for healthy pregnancy and delivery. There also is increasing evidence that particular stress that is associated with on-going racism may affect black women's reproductive health adversely. Future research must be theory based, take into account the complexity of measuring stress, and include a comprehensive biobehavioral assessment and measurement of potential confounding and effect modifying factors.

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