# Title page

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**Optimizing Pregnancy Outcomes in Minority Populations**
Edited by Yvonne Bryan, Thelma Patrick

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The recently announced National Institutes of Health Roadmap underscores that the growing complexity of modern biomedical research will require new methods of discovery. Today’s scientists must “move beyond the confines of their own discipline and explore new organizational models for team science,”¹ using an interdisciplinary approach that can yield fresh and possibly unexpected insights. Consistent with this vision, in March 2003, the National Institute of Nursing Research (NINR) convened a diverse working group of scientists and clinicians to address “Optimizing Pregnancy Outcomes in Minority Populations.” Premature and low birth weight (LBW) births remain a major public health problem and a significant contributor to health disparities. Incidence data reveal that the rate of prematurity and LBW among black infants is roughly twice that of white infants, with wide variance among minority groups and subgroups. Premature and LBW infants often require prolonged hospitalization and intense intervention. Findings from NINR-supported research have added evidence that, later in life, these children may experience a higher incidence of developmental delays, chronic health problems, and poor school performance.²-⁴

The Optimizing Pregnancy Outcomes Working Group brought together experts in public health, psychology, epidemiology, basic science, clinical medicine,
and nursing with an established track record in the study of high-risk pregnancy and birth outcomes or in the design of related disease pathways and biomarkers. The 2-day meeting included presentations on the current state of research on pregnancy in minority populations, psychosocial and behavioral influences, stress and neuro-endocrine mechanisms, maternal health, environmental factors, and physiologic pathways. Lively discussions followed each presentation, as the working group members explored the state of the science and added their own expert perspectives on the problems. Important themes included conceptual dimensions of epidemiologic factors and risk in relation to minority populations, along with methods, measurement, and design issues that are associated with biobehavioral research. Many participants provided specific insights regarding biobehavioral issues in human-environment interaction, stress and health status relationships to risk, maternal-fetal interactions, and the complications of pregnancy. Out of these discussions, the participants formed recommendations about future directions and possible models that can help to develop, test, and refine new knowledge.

This supplement presents papers from several of the participants of the interdisciplinary working group on major topics of concern in this area:

Susan Gennaro provides an overview of the problem and a review of the effects of education, socioeconomic status, race and ethnicity, health care delivery, and health behaviors.

Ellen Silbergeld and Thelma Patrick review the effect of environmental exposure, which is a tangible measure of health disparity.

Jennifer Culhane and Irma Elo describe social and health problems by using the neighborhood as a specific environment.


Robert Goldenberg, Alice Goepfert, and Patrick Ramsey discuss the issues that are related to the use of biomarkers as a means of describing the mechanisms of pregnancy complications.

Carol Hogue and Douglas Bremner delineate racism as a specific stressor.

Patricia O’Campo and Ashley Schempf address the problems of measuring psychosocial constructs.

To conclude this supplement, the working group co-chairs Thelma Patrick and Yvonne Bryan provide a synthesis of the discussions and recommendations for future biobehavioral approaches to this growing and perplexing public health concern and stress the importance of working collaboratively toward solutions.

NINR is confident that these papers will contribute to the current understanding and the future research strategies needed to move science forward in the areas of high-risk pregnancy, prematurity, and LBW in minority populations. The results from this working group are the latest, but not the only, recent efforts directed toward the resolution of issues in these areas. The unique quality of this group came from the mix of diverse experts who previously may not have been in dialogue with one another but who left this meeting intent on developing collaborative strategies for future research.

NINR looks forward to further collaborations across the National Institutes of Health and other agencies to achieve the vital aims of this working group in improving the care of pregnant women from minority populations toward the goals of reducing health disparities, improving birth outcomes, and decreasing the rate and the complications of prematurity and LBW.

References

Overview of current state of research on pregnancy outcomes in minority populations

Susan Gennaro, DSN, RN*

School of Nursing, University of Pennsylvania, Philadelphia, Pa

Pregnancy outcomes improved significantly over the 20th century in the United States but currently vary widely between women of different ethnic and racial backgrounds. The current health disparities that exist are based, in part, on differences in socioeconomic status or education. There is wide variability in pregnancy outcomes within specific subgroups of women. Disparities may be due to underlying differences in health before pregnancy, differences in community norms, and individual lifestyle choices and to differences in health care delivery systems. Areas for needed research and promising new models of care are reviewed.

The United States has enjoyed marked improvements in the health of mothers and babies during the 20th century. In 1900, approximately 6 to 9 women died for every 1000 live births. For every 1000 live births in 1900, approximately 100 infants died before they reached their first birthday. Over the course of the 20th century, the infant mortality rate declined by >90% to a rate of 7.2 per 1000 live births. Maternal mortality rates declined by 99% to a rate of 0.1 reported deaths per 1000 live births (7.7 deaths/100,000 live births in 1997). These marked changes in pregnancy outcomes occurred as a result of a better medical and nursing care. Early in the century, the establishment of prenatal care, well baby care, and family planning services improved pregnancy outcomes. In the second half of the 20th century, improvements in the treatment for mothers and babies were enhanced by the establishment of perinatal regionalization and high-risk perinatal and neonatal units.

However, throughout the 20th century, improvements in the health of mothers and babies also occurred because of improved economic and social welfare, changes in lifestyle that included improved nutrition, improvements in education, and decreased environmental threats.

At the beginning of the 21st century, we can be proud of all that has been accomplished to improve pregnancy outcomes. However, we must be concerned about inequities that continue to exist and the challenges that still remain in promoting optimal outcomes. Not every woman enjoys the same likelihood of positive pregnancy outcomes. Well-documented disparities in pregnancy outcomes exist between racial and ethnic groups. The widening gap, over the past century, in both infant and maternal mortality rates in black infants compared with white infants is of particular concern. Black infants are more than twice as likely to die as white infants. Black mothers are 3 times more likely to die than white mothers.

To eliminate health disparities in pregnancy outcomes, it is important to be able to identify (1) where disparities exist, (2) what disparities might be most amenable to changes in economic situation, (3) where improvements
in medicine and nursing may be expected to most improve pregnancy outcomes, and (4) where individual life style changes can most significantly interact with improved health care to improve pregnancy outcomes. The purpose of this study was to provide an overview of the current state of pregnancy outcomes and health disparities, to discuss promising research strategies and findings that might serve to narrow the gap in health disparities in pregnant women and their infants on the basis of race and ethnicity, and to discuss the challenges that must be faced as these disparities are narrowed and then eliminated.

Overview of the literature

Current state of health disparity and pregnancy outcome

Black women compared with women of other races or minority background are most likely to die from pregnancy-related complications, to have a fetus or infant who dies, or to have a preterm or low birth weight infant, and to be delivered of an infant with congenital anomalies. Black women are also more likely than other women to experience a spontaneous abortion, an ectopic pregnancy, or a cesarean delivery.

Although black women are most likely to experience the most negative pregnancy outcomes and white women generally experience more positive outcomes, there is variability among specific pregnancy outcomes between different ethnic and racial groups. For example, in 1998 the infant mortality rate was actually lowest for Asian/Pacific Islander women at 5.5 per 1000 live births. The infant mortality rate in 1998 was 5.8 per 1000 live births for Hispanic infants, 6.0 per 1000 live births for white infants, 9.3 per 1000 live births for Native American infants, but 13.8 per 1000 live births for black infants. Black women in 1998 delivered a higher percent of low and very low birth weight babies (13%) than did any other ethnic or racial groups. This 13% low birth weight rate for the infants of black women was double the 6.4% that was experienced by non-Hispanic white women, the 6.5% that was experienced by white women, the 6.8% that was experienced by Native American women, or the 7.4% that was experienced by Asian/Pacific Islander women.

Not only are black infants most likely to die, but their mothers are also at highest risk for death as a result of pregnancy. The pregnancy-related maternal death rate (deaths that occur during pregnancy or within a year of pregnancy as a result of pregnancy) between 1991 and 1997 was 11.3 per 100,000 live births overall in the United States. It was lowest in white women at 7.3 and highest among black women at 29.6. This 3 to 4 time higher death rate for black women than for white women strikingly delineates the health disparities that exist today in pregnancy outcomes. Other minority groups are also at increased risk for maternal pregnancy-related death. American Indian/Alaska Native women have a pregnancy-related mortality rate of 12.2, whereas Asian/Pacific Islander women have a rate of 11.3 and Hispanic women have a rate of 10.3.

Variability within subgroups in pregnancy outcome

Clearly, disparities exist in pregnancy outcome that is based on racial or minority status, but the causes of these disparities and therefore the solution to the problem of health disparities is less clear. There is a well-known wide variation in pregnancy outcomes even within specific ethnic or racial groups, which argues for careful examination of the meaning of race and ethnicity. Factors also must be examined that might interact with minority status to influence pregnancy outcomes (such as individual health behaviors, education, income, and other sociodemographic variables).

Differences in smoking behaviors, for example, among Hispanics subgroups might help to explain some of the variability in low birth weight and very low birth weight births within this group. Low birth weight is lower among Mexican American infants (6%) than among Puerto Rican infants, who at 9.7% are one of the minority groups with the highest rates of low birth weight. Mexican American women as a group have low smoking rates, high levels of social support, and generally are well nourished. These factors may contribute to the decreased risk of low birth weight that Mexican American women experience compared with other Hispanic subgroups.

As a group Mexican American women also have low levels of education, less timely attendance at prenatal care, high poverty, and high teenage pregnancy. Mexican American women also have relatively positive pregnancy outcomes, which perhaps indicates that the modification of health behaviors can be beneficial particularly in women who are at risk of experiencing poor pregnancy outcomes. Promoting community norms for healthy life styles among minority populations and promoting positive individual health behaviors may result in important public health gains. Currently, minority women perceive that they are less likely to receive health-promoting messages during prenatal care, including information about smoking cessation and alcohol use. Health care providers may provide care that is intentionally or unintentionally biased and that does not account adequately for and promote individual and community strengths. Thus, differences in the care that is provided may explain, in part, some of the disparities in pregnancy outcomes that currently exist between women of varying racial and ethnic backgrounds.
The variability in pregnancy outcomes that exists within subgroups of the same broad ethnic or racial group provides support for continuing to collect more specific data on race, ethnicity, and health outcomes on birth certificates, death certificates, and other sources of large-scale survey data. To truly understand how to intervene to eliminate health disparities, it is important that we better understand differences in pregnancy outcomes in specifically defined ethnic and racial groupings. For example, in Hispanic women, not only do pregnancy outcomes differ depending on the original country of origin, but there also are known differences in pregnancy outcomes between women who were born in the United States and those born women who were born outside of the United States. Hispanic women who were born outside of the United States have a 50% higher pregnancy-related mortality rate than do women who were born in the United States. Natality also has a variable influence on infant outcomes, with foreign-born Hispanic women being less likely to be delivered of low birth weight infants compared with US-born Hispanic women. Again, this points out the importance of health behaviors such as not smoking, nutrition, social support, and other culturally based protective factors.

Natality in other minority women has also been examined to help explain whether pregnancy outcomes are more likely to be explained by economic factors (generally less favorable among recent immigrants), by genetic factors (that would be unaffected by place of natality), or by life style and health care variables that may be interrelated with economic situation. Black women who were born in Africa have been shown to have birth weight patterns closer to those of US-born white women than to US-born black women. This advantage of foreign birth in black women was also found in a group that was largely born in the Caribbean (72%) and may be explained in part by the better prepregnancy nutritional status that is found in the foreign-born women in this study. Thus far, foreign-born Asian women exhibit the same kinds of birth weight patterns that US-born Asian women experience. These findings raise questions about the genetic basis of differences in pregnancy outcomes and lend support to the need to identify and modify environmental factors (such as poverty and poor working conditions) that lead some groups to be more likely to experience poor pregnancy outcomes than other groups. The fact that there is more genetic variation within races than between them and the historically changing social constructs that surround our definition of race also raise questions about the likelihood that genetic differences explain disparities in pregnancy outcomes. However, genetic variations cannot be discounted fully. Infant death is influenced by documented differences in the response of white and black infants of similar birth weights and gestational age to surfactant therapy, for example, that may be explained in part by poorly understood racial differences.

Poverty, education, and pregnancy outcomes

In the United States, race and minority status has long been associated with social class and with socioeconomic status both in terms of income and education. It is clear that social class is related inversely to pregnancy outcomes. Black, Hispanics, and Native American individuals are represented disproportionately among the poor. However, the extent is not clear to which disparities in pregnancy outcomes persist, even in more optimal socioeconomic situations.

In a large study of low income black and white women, the black women had more preterm and low birth weight infants than the white women, even though many of the risk factors for low birth weight were more common among the white women. However, the black women in this study were poorer and less likely to be married.

The contribution of income to pregnancy outcomes has been examined in military populations in which pregnant women do not have financial barriers to health care and income is well documented. Black women in the military have better pregnancy outcomes than black women in the general population. However, disparities in pregnancy outcomes exist between black and white enlisted women. For example, black enlisted women had a higher probability of preterm delivery (13.5%) than did white women (10.5%), but this difference was seen only in early preterm delivery before 33 weeks of gestation. Wives of enlisted men who had similar access to prenatal care, similar income, and the benefit of social support from a husband were also found to have disparate birth outcomes based on race. Low birth weight was twice as likely in black mothers as in white mothers.

When large metropolitan areas were examined, the black-white difference in infant mortality rates was found to be smaller in areas with low segregation, even when considerable differences existed in poverty levels between black and white women. These findings once again underscore the concern that being black in the United States has an impact on health that is not solely accounted for by socioeconomic status.

Similarly, the discrepancy in pregnancy outcomes between black and white women remains even among college-educated women. Education is generally expected to result in better health outcomes. Educated women are more knowledgeable about how to promote a healthy pregnancy. However, college-educated black women continue to experience higher rates of low birth weight than college-educated white women. If a black infant is born at normal weight, there is no difference in
the infant mortality rate, including the number of sudden infant death syndrome deaths between black and white children of college-educated parents. The rate of low birth weight remains twice as high in black infants of college-educated parents as in white infants of college-educated parents. These disparities again underscore the need to examine factors other than socioeconomic status in an explanation of health disparities.  

**Underlying health problems and pregnancy outcome**

Whether because of basic biologic differences, lifestyle factors, or differences in diagnosis and treatment, there are underlying health problems that are more common in some groups of women than in others. These underlying health problems might influence pregnancy outcomes. For example, anemia may be more common in minority women. One study of 8903 women found that anemia was one of the major underlying causes of prematurity among black women. However, other studies have not found anemia to be related to birth outcomes in minority populations. 

Known differences in maternal hypertension between different ethnic and racial groups might help to explain differences in disparities in pregnancy outcomes. Chronic hypertension that precedes pregnancy is higher among black women than it is for women of other ethnic or racial status. Women with chronic hypertension are known to be 4 times more likely to have preeclampsia and eclampsia. Hypertensive black women are also at 3-fold greater risk of experiencing antepartum hemorrhage that also contributes to preterm delivery and low birth weight.

Many lifestyle choices are related to health problems that may influence pregnancy outcomes. Poor nutrition, smoking, drug and alcohol use, and a sedentary lifestyle have all been related to cardiovascular health, diabetes mellitus, and a myriad of other health problems that lead to poorer pregnancy outcomes. 

Black women as a group are less likely to engage in regular exercise than other groups of women. Regular exercise has been demonstrated to decrease the risk of gestational hypertensive disorders, and a lack of exercise may contribute to hypertension in pregnant women who are at risk for hypertension. There also may be underlying differences between majority and minority groups in what they eat, their patterns of weight gain during pregnancy, and their patterns of nutrient intake during the day that contribute to increased poor pregnancy outcomes in minority women. Smoking during pregnancy in minority women has been demonstrated to increase the risk for preterm delivery and low birth weight.

**Health care delivery system factors and pregnancy outcome**

The impact of the health care delivery system on health outcome has received much attention of late. The interaction between those seeking health care and health care providers may differ systematically between women of majority and minority status, as seen in the lack of health promotion information provided to black women. There is a well-documented shortage of health care providers who are from minority populations, which also may add to the disparity that exists in pregnancy outcomes between majority and minority women. For example, racial and ethnic disparities have been found to exist in the rates of cesarean delivery even when clinical indications and insurance are taken into consideration. Additionally the content of prenatal care received by black and white women in the United States has been demonstrated to differ in terms of the use of tocolysis, ultrasound examination, and amniocentesis. Black women are less likely to experience amniocentesis or ultrasonographic examinations, and there is an underused of tocolysis among black women with singleton pregnancies.

Race and gender have been demonstrated to be important factors in the way that patients and providers interact and with patient satisfaction. Patients who are cared for by members of their own racial or ethnic subgroup are least likely to encounter problems with culturally sensitive care, which includes miscommunication, inherent racism, or medical decision-making that is unintentionally influenced by patient background. The development of a culturally competent health care delivery system may mean not only increasing the number of minority health care providers but also the development of systems of care that are acceptable to and address specific health needs of minority populations.

**Overview of current promising research strategies and findings**

**Research on the cause of poor pregnancy outcome**

Continued research on the cause of preterm birth, low birth weight, and other poor pregnancy outcomes is needed. We have not been successful in decreasing the preterm birth rate or low birth weight rates in part because the causes of these problems are not clearly understood. As well as continuing to elucidate the underlying cause of poor pregnancy outcome, we continue to need research that carefully examines the effectiveness of the interventions that we are currently using. Many of these interventions (such as bed rest) may have unacceptable sequelae to the very women that they are prescribed to help.
Even with similar education and similar income there are well-known differences between the races in family wealth and family social status, so findings that income and education do not eliminate disparities in pregnancy outcomes are not altogether surprising. However, the fact that, when income and education is controlled, disparities in pregnancy outcomes between majority and minority populations persist indicates that factors other than poverty contribute to poor pregnancy. The stress of racism, intergenerational differences in health, differences in how the health care system responds to individuals of different racial backgrounds, and biologic variables (such as blood pressure control during pregnancy or infection) that may be mediated by these other factors must be examined carefully if we are to be able to respond adequately to the racial disparities that exist in pregnancy outcomes. For example, racial and gender discrimination has been documented to lead to negative psychologic and physiologic outcomes (such as increased stress and increased blood pressure, both of which could negatively influence pregnancy outcome).

Chronic stress has also been associated with the increased likelihood of experiencing infections (such as bacterial vaginosis, which is another leading cause of adverse perinatal outcome). Increased stress itself has been related, independent of medical risk, to both preterm delivery and low birth weight. Ethnic differences in corticotropin-releasing hormone during the second trimester of pregnancy underscore the importance of continued examination of the relationship between stress and pregnancy outcome in women of varying ethnic and racial backgrounds. Research that clarifies the relationship of stress, individual health behaviors, and health outcomes among varying ethnic groups is particularly important, given recent research that has linked increased stress to decreased immune function and preterm birth.

Research on health behaviors

Culturally competent care that is successful in improving individual health behaviors without “blaming” individuals for health care choices (such as overeating, drinking, smoking, when these behaviors may be particularly helpful in reducing the stress of poverty) will be particularly important in the 21st century. Although nutritional variation in a large sample of 4589 US women was not found to explain ethnic differences in birth outcomes, factors other than the intake of major nutrients may be related to ethnic and racial differences in pregnancy outcomes. For example, research that links vitamin C and E to preterm premature rupture of membranes argues for a continued examination of the relationship between nutrition and pregnancy outcomes, especially in terms of micronutrients.

Patterns of nutritional intake may influence pregnancy outcomes. There are documented differences in patterns of weight gain during pregnancy among women of various racial and ethnic subgroups that might make some women more susceptible at certain points during pregnancy to negative outcomes. On a day-to-day basis, prolonged periods without food intake have been related to elevated maternal corticotropin-releasing hormone and may be related to risk for preterm delivery. Clearly, changing health behaviors (such as smoking and drug and alcohol use) has the potential for large payoffs in the improvement of both maternal and infant health, but research is needed that provides direction for how best to change these behaviors in pregnant women.

Health care delivery systems

Just as changes in health care delivery systems in the 20th century led to improvements in pregnancy outcomes, research on culturally competent health care systems must be developed and evaluated in the 21st century. Prenatal care has been demonstrated to improve pregnancy outcomes. Improved insurance coverage in the late 20th century led to significant improvements in prenatal care use among poor women but did not result in improved pregnancy outcomes (such as fewer low birth weight births). Given constraints of time and resources, findings that many minority women report not receiving information on sexually transmitted diseases, preterm birth prevention, family planning, or family violence is not surprising but might help, in part, to explain why improving prenatal care usage is not sufficient to improve pregnancy outcome. Enhanced models of prenatal care delivery, preconceptual care, and new models of patient education that are targeted specifically to the needs of minority populations may be needed to ensure further improvements in some of the most intractable of health problems.

Many new models of health care delivery are being developed and evaluated. For example, a telephone support program that is provided by nurses decreased the rate of preterm birth in black women compared with white women in one southeastern study. Programs that provide home-based care or peer support may also be efficacious with minority populations.

Potential research questions and challenges

A number of interacting factors clearly contribute to the poorer pregnancy outcomes that are experienced in minority populations. Examining individual environmental, health, and societal factors that all contribute to pregnancy outcome is clearly necessary. Studies that
examine interactions of those factors that are most likely to contribute to poor pregnancy outcomes must be conducted. A number of studies currently are examining models of social, behavioral, physiologic, and psychologic factors that may explain poor pregnancy outcomes in minority populations.\(^7^6,7^7\) For example, exposure to environmental pollution and toxins is experienced more often by minority women, who might also be most likely to experience poor nutrition and increased stress, which further enhances the impact of environmental toxins.\(^7^8\)

Paternal exposure to solvents has been related to increased low birth weight,\(^7^9\) and future studies that examine paternal and maternal exposure to environmental risks may be one fruitful area for further study.

Just as in the 20th century, improvements in maternal child health have occurred in part because of improvements in social factors; social factors in the 21st century continue to warrant close investigation. For example, pregnancy desire has been found to be related to low birth weight; women who did not want to be pregnant had higher rates of low birth weight.\(^8^0\) One reason that women do not seek early prenatal care is that they do not wish to be pregnant, and this may impact on individual health behaviors (such as smoking, drinking, and drug use). Research that identifies interventions to help women work through issues that surround the discovery of pregnancy may be particularly helpful in the promotion of healthy pregnancy behaviors. Women who do not want to be pregnant are more likely to smoke, drink, have unsafe sex, eat poorly, get inadequate folic acid, and thus have poorer outcomes.\(^1\)

In this same vein, research on novel ways to improve preconception education and reproductive health such that more women take folic acid, receive appropriate vaccinations, and practice other health-promoting behaviors would seem to be particularly appropriate. With so many new ways of providing education for women, we are at a point in time at which we will be able to provide much wider and more targeted health education in a much more cost-effective manner than we have been able to in the past, and we must examine ways to best do this.

In the 21st century, prevention and treatment modalities that improve pregnancy outcomes for all women must be developed. New systems of health care delivery that promote healthy pregnancies and that are sensitive to the needs of specific communities also must be established. However, meaningful improvements in maternal and infant health will require more than improved medicine, nursing, and health care delivery systems. Meaningful improvements in maternal and infant health will also require, as they did in the 20th century, improved economic situations, education, and lifestyle changes and a decrease in environmental risks. Continued research on the multifactorial nature of poor pregnancy outcomes will require unique collaborations between researchers from different disciplines and with stakeholders from varying communities. At the end of the 21st century, just as at the end of the 20th century, continued marked improvements in maternal and infant outcomes will be made, but this time for all women, not just for some women.

References


Environmental exposures, toxicologic mechanisms, and adverse pregnancy outcomes

Ellen K. Silbergeld, PhD,a,* Thelma E. Patrick, PhD, RNb

Johns Hopkins University, Bloomberg School of Public Health, Baltimore MD,a and University of Pittsburgh School of Nursing, Pittsburgh, Pa

KEY WORDS
Environment
Reproductive health
Outcome
Fetal development
Toxic agent

Environmental risk factors (defined as those agents and stresses that are generally the responsibility of environmental agencies) are often tangible indicators of economic and social disparity in the United States. Many site-specific analyses have reported that communities of color and poverty are exposed more often and more intensively to such environmental hazards as lead, air pollution, agrochemicals, incinerator emissions, and releases from hazardous waste sites. Thus, exposures to these toxicants may explain part of the socioeconomic disparity that is observed in terms of risks of adverse pregnancy outcomes. The purpose of this study was to describe the associations between certain environmental exposures and reproductive outcomes through a discussion of both epidemiologic and animal model studies. In addition, we list potential sources of exposure data and describe physiologic changes in pregnancy that may increase the likelihood of both external exposures and increased internal dose. Several models for further study of environmental risk factors are suggested to increase our understanding of gene-environment interactions toward the goal of indentifying preventable risk factors to improve reproductive outcomes of particular concern to disadvantaged populations.

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Among the health risk factors that are associated with poverty and discrimination in the United States, unequal exposures to many environmental risks are often among the more tangible measures of disparity. The concept of environmental justice, or environmental racism, is based on the frequent observation that environmental risks and social injustice coincide; it is often dated to 1982, when a community of color in Warren County, NC, drew the explicit linkage between racism and environmental risk during organizing to block a hazardous waste dumpsite.1 Although the relationship between community ethnicity and/or economic disadvantage with increased risks of environmental exposures is complex, especially as to sequence,2 analyses of this association may be valuable in the explanation of part of the gradient in health status that is observed for different sociocultural groups in our society.3-5 Many site-specific analyses have reported that communities of color and poverty exposed are more often and more intensively to such environmental hazards as lead, air pollution, agrochemicals, incinerator emissions, and releases from hazardous waste sites.6-10 This overlay of environmental risks with poverty and disadvantage has also been reported in Brazil, Germany, and other countries.11-13 In the recent past, the recognition and alleviation of environmental injustice has elicited specific policy responses from the Environmental Protection Agency.
Many environmental risks that disproportionately affect disadvantaged communities are more likely to affect women and children. Poverty is itself a women’s health issue; thus, when poverty is associated with increased risks of exposure, these risks may fall more heavily on poor women. As shown in Table I, there is a high correlation in Maryland between the prevalence of poverty and the percentage of housing with high risks of exposure to lead from deteriorated lead paint. In fact, income and ethnicity are generally used as predictors of lead exposure. The Centers for Disease Control and Prevention uses such predictors in its guidelines to health departments and health practitioners for justifying selective, rather than universal, childhood blood lead screening. Similarly, Wing found that county income and percentage of minority population are good predictors of the density of large-scale hog-producing facilities (so-called factory farms) in North Carolina and Georgia.

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* Data from the US Environmental Protection Agency and the Centers for Disease Control and Prevention, available at: www.scorecard.org.

Like other adverse health outcomes, environmentally acquired health risks are increasingly recognized to involve gene-environment interactions. That is, we know now that non-genetic events modulate those conditions that were thought to be “purely” genetic in the past. Likewise, it is recognized that individual responses to acquired risks may be augmented or diminished by genotype. This concept provides new opportunities for understanding the role of environmental risks in pregnancy outcomes. The consideration of more complex models of cause and causation is exemplified by recent studies on folate and genotype.

Given the importance of pregnancy to an individual and society, it is not surprising that environmental risk factors are the subject of great public concern, research, and government regulation. Recent landmarks in public concern in the United States over potential environmental risks to pregnancy, and government responses to such concerns, include Proposition 65 (a landmark law in California that requires the disclosure of exposures “known to the State of California to be carcinogenic or reproductive toxicants”), the worldwide focus on the identification and control of endocrine disruptors (chemicals that interrupt endogenous hormone signals); and the proposal for a national children’s longitudinal health study. The aforementioned issues are under considerable debate among the scientific and political community.

Before turning to the subject of this article, it is appropriate to consider the question: Is pregnancy only a woman’s health issue? It is assumed often that the only adverse reproductive outcome of paternal exposures is a reduction in fertility because of reduced sperm number or quality that results from spermatotoxicity or endocrinologic dysfunction. However, epidemiologic studies have reported associations between paternal exposure and adverse developmental outcomes in surviving children. Standard toxicologic studies usually do not study the male parent separately; early embryonic death is the most common outcome that is assessed in studies of the male patient (measured in toxicity studies as dominant lethality). Other toxicologic studies of chemicals and drugs have found the effects of male exposure on morphologic abnormalities in rodent embryos and increased preimplantation loss. One such chemical is acrylamide, which is a widely used industrial chemical that recently has been found to be a combustion byproduct in many fried foods.

### Sources of information

Information on chemical exposures is available from several sources. Of greatest interest, the Centers for
Disease Control and Prevention National Center for Environmental Health recently has conducted national exposure assessments of women of childbearing age in its periodic population-based surveillance with the use of the design of the National Health and Nutrition Evaluation Surveys and ultratrace analyses of blood to assess exposure to environmental chemicals that are of high concern.36,37 Such surveys have revealed continued exposure to major reproductive toxicants such as lead, organochlorine insecticides, methyl mercury, cigarette smoke (cotinine), organophosphate pesticides, and certain organic solvents (Table II). These data can be of very great relevance to research on the associations between environmental risks and adverse pregnancy outcomes and other end points of importance to women.

Table II  Organophosphate Pesticide Metabolites in Urine of Americans37

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>By age (y)</th>
<th>By sex</th>
<th>By race</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1998)</td>
<td>6-11</td>
<td>12-19</td>
<td>20-59</td>
</tr>
<tr>
<td>µg/g Creatinine (µg/g)</td>
<td>13.0a</td>
<td>21.0</td>
<td>22.0</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*a Dialkylphosphate metabolites, expressed as microgram per liter and b micrograms per liter corrected by creatinine.

Information on the sources of these and other environmental exposures is available from the Environmental Protection Agency (particularly on pesticides and industrial chemicals) at www.epa.iris.gov and the Agency for Toxic Substances and Disease Registry (with an emphasis on exposures that are associated with hazardous waste sites).

An additional source that is operated by a nongovernmental organization (Environmental Defense) is accessible on the worldwide web (www.scorecard.org) and contains not only inventories on toxic contaminants but also provides geographic information on source locations. Environmental Defense also contains highly useful links to authoritative databases on toxicity and risk assessments. The National Institute of Occupational Safety and Health operates the Registry of Toxic Effects of Chemical Substances, which focuses on chemicals in the workplace. Material Safety Data Sheets are also available through the National Institute of Occupational Safety and Health; such data sheets are more useful for information on acute exposures and emergency response. The International Program on Chemical Safety of the World Health Organization provides web-based access to short and long evaluations of chemical hazards, which include excellent information on sources and methods of diagnosis. TOXLINE is a program within the National Library of Medicine that provides online access to reviews and the biomedical literature on chemical hazards through PUBMED. Information that is specific to reproductive hazards is also available from several sources. REPROTOX, part of MICROMEDIX, contains highly valuable information for clinicians and health providers. The National Toxicology Program of the National Institutes of Health provides a limited inventory of more comprehensive toxicity assessments, which include evaluations of both epidemiologic and toxicologic studies on reproductive hazards.

Exposures during pregnancy

Pregnant women may be exposed to the same environmental chemicals and activities as are nonpregnant women or as they were before their pregnancies.38,39 Although generalizations are dangerous, there are some aspects of the lives of many women that increase the likelihood of exposures to certain toxic agents. For example, as compared with men, many women may spend more time at home, either as homemakers and family caregivers or as self-employed home-based workers.39 The home environment can be the source of specific toxicant exposures (eg, indoor air quality).40 Rudel et al41 have reported high levels of pesticides that are used in the home and chemicals that are released from consumer products. Some home-based activities (such as gardening and craftwork) can involve exposure to toxic agents under conditions with less control than many regulated workplaces. For example, in the Baltimore Washington Infant Study, exposure to certain pesticides were reported more frequently from home use by women than by men in occupational settings.42 Crafts (eg, making jewelry, ceramics, prints) can involve hazardous chemicals that included lead-based solders, metal-containing glazes (lead, manganese, uranium), and solvents in poorly ventilated spaces.43 One of the most dramatic recent examples of home exposure occurred in California, when several members of a family (which included an infant and mother) died as a result of the use of mercury to recover gold.44
There are also some behavioral and biologic aspects of pregnancy that may intensify or increase the likelihood of exposure. Behaviorally, many women (and men) prepare for expected children by making repairs to the home environment. Home remodeling may increase exposure to hazards such as lead-based paint, asbestos, formaldehyde, and radon.\(^{45}\) Of these, lead is a major reproductive toxin that can cause decreased fertility in men and women and increase the risk of intrauterine toxicity to the fetus.\(^{19}\)

Geophagy (dirt eating) is practiced by some women during pregnancy. Geophagy most likely originates from a rational strategy to obtain the iron and calcium that are necessary to maintain a healthy pregnancy under conditions of iron- and calcium-poor diets in some traditional African societies.\(^{46}\) However, in modern US environments, geophagy can be a risky behavior because of the high levels of metals in many urban soils, which results from metal use in gasoline and paints.\(^{47,48}\) The old urban hazards of lead in gasoline are now being replicated by the use of manganese additives.\(^{49}\)

Some folk medicines are consumed during pregnancy, particularly for morning sickness. Among these, greza and azarcon (used by some Hispanic communities) contain high concentrations of lead.\(^{50}\) Bint al zahab (or dhahab) is a traditional medicine in some Arabic communities; this lead-oxide compound is often burned in the bedroom.\(^{51}\) Mercury is an ingredient in Mexican beauty creams,\(^{52}\) and elemental mercury is used in ritual practices by some Caribbean groups.\(^{53}\) These practices have resulted in episodes of frank lead or mercury intoxication, with probably many more unreported.\(^{52,54}\)

Biologically, there are physiologic changes that occur in normal pregnancy that may affect exposure and internal dosage. These may involve changes in gut absorption or the mobilization of toxic chemicals that previously were encountered in the woman’s environment and stored in her body. Mobilization of stored toxic chemicals may be exacerbated under conditions of nutritional deficiencies: Diets that are lower in calcium are known to increase bone-lead mobilization during pregnancy and lactation in animal models\(^{55}\); very low fat diets may increase the draw on body adipose stores during lactation. Two broad classes of chemicals can be involved in this process: (1) chemicals that are stored in bone are subject to demineralization and chemicals that are stored in fat are subject to fat mobilization.\(^{56}\) Among the bone seekers, lead and cadmium are known to be mobilized back into blood during pregnancy.\(^{57,59}\) This mobilization is driven by 2 phenomena: blood volume expansion early in pregnancy and fetal skeletal development in late pregnancy.\(^{57,58,60,61}\)

Pregnancy-associated bone-lead mobilization is likely to have been the cause of the phenomenon acutely observed by Sir Thomas Oliver, in 1911, when he wrote of women who worked in the lead industries, that “pregnancy seems to make lead poisoning worse.”\(^{62}\) He also noted reports of more frequent miscarriage among women exposed to lead. Gulson et al\(^{56}\) have found that bone-lead stores may contribute as much as 33% to maternal blood lead levels during pregnancy and lactation. Maternal-fetal blood-lead levels are nearly equivalent, so this remobilization contributes to prenatal lead exposure.\(^{63}\) However, this mobilization may also be hazardous to maternal health.\(^{38}\) Increases in blood lead during pregnancy have been associated with an increased risk of hypertension in pregnant women.\(^{64}\) Cadmium, another toxic metal that also is stored in bone tissue, can exacerbate the osteopenia that is experienced by pregnant women through its toxic effects on mineral metabolism.\(^{57}\)

Lipophilic chemicals (which include the pesticides DDT, chlordane, aldrin, methoxychlor, and dieldrin, polychlorinated biphenyls (PCBs), and chlorinated dioxins) are stored in body fat for decades after exposure.\(^{56}\) During pregnancy and lactation, these fat stores may be mobilized and release the chemicals that are contained in them. Again, like many toxic metals, these chemicals can also pass the placental barrier, which results in intrauterine exposure of the fetus. Reproductive and developmental toxicity has been associated with such exposures that occur both before and during pregnancy, in 2 human cohorts (the Yusho group in Japan and the Yucheng group in Taiwan\(^{65}\)). The effects of remobilized halogenated hydrocarbons on women’s health has not been investigated extensively, although exposure of breast tissue to chemicals in breast milk has been suggested to play a role in increasing risks of breast cancer.\(^{56,67}\)

**“Sensitive windows” for environmental risks**

Developmental and reproductive toxicology run together, because in many respects the health and integrity of the reproductive system is influenced by prenatal events. In some cases, the consequences of prenatal exposure are expressed immediately or in early postnatal life. In other cases however, prenatal exposure can influence structural and functional status of the reproductive system later in life. For example, the reproductive life span in women is determined by the number of oocytes in the ovarian pool and the number of oocytes that are available over the lifespan for recruitment, maturation; and ovulation is determined prenatally. In animal models, early reductions in total oocyte number by chemical exposures result in premature loss of fertility.\(^{68}\) In mice, exposure to chemicals in cigarette smoke can reduce oocyte number\(^{69}\); in women, smoking has been associated with earlier age of menopause.\(^{69}\)

Many other aspects of sexual behavior and function are also determined significantly prenatally by an
interplay of genes and endocrine function. Exposure to elevated hormones, from either endogenous or exogenous sources, can alter the development of the reproductive tract, with devastating effects on a woman’s ability to carry a pregnancy to term and sex-typic behaviors in adulthood. For that reason, consideration of “sensitive windows,” or periods of increased response to exogenous exposure, is appropriate for the evaluation of the responses of both the fetus and reproductive health in later life (Figure 1).

Increased sensitivity to the effects of toxic agents on the development of the reproductive system can result from several developmentally transient factors: specifically timed developmental events (such as the interplay between Mullerian and Wolffian structures in the developing vagina),70 the ability of chemicals to reach the fetus (such as lead transfer into the fetal circulation),59 and the developmentally related expression of specific proteins (such as the induction of the activation/deactivating enzymes of the P450 family).71 For fetal development, the preimplantation stage is a time in which many, if not most, fertilizations fail to progress to fetuses.72 Environmental agents may interfere with these early stages of intrauterine development by altering the early genetic program of embryos or by affecting the uterine milieu by inducing endometriosis or altering hormonal function.72-75 Later in gestation, the lengthy process of genetically programmed human organogenesis provides many opportunities for toxic interactions affecting the mother and/or the fetus.

Reductions in fertility

Exposure before conception may affect pregnancy outcomes primarily by hormonal dysregulation or germ cell toxicity in either parent. In animal models, chemicals that deplete ovarian follicles (such as the pesticide vinclohexene) are known to reduce the age of onset of menopause and affect cyclicity,76,77 thus reducing fecundity and increasing the likelihood of subfertility (defined as a prolonged time to pregnancy with unprotected intercourse). Fertilizability of oocytes can also be affected adversely by exposure to toxic chemicals, as reported in studies of rats that were exposed to either of the solvents trichloroethylene or tetrachloroethylene.78 Chemicals (lead, for example) that suppress hypothalamic-pituitary-gonadal regulation of reproduction in both men and women may also reduce fertility. In men, occupational exposure to the highly estrogenic pesticides chlordenecon and dibromochloropropane has caused azospermia and infertility.55,73

Pregnancy loss, spontaneous abortion, and miscarriage

After fertilization, pregnancy may fail because of the loss of the embryo or fetus. Early pregnancy loss is a relatively common event, although it often goes undetected.72,79 Because of this finding, associations between environmental risk factors and increased risks of early pregnancy loss or miscarriage are often difficult to discern.72 The clearest evidence of an association that involves early miscarriage can be found in epidemiologic studies of exposure to smoking (including second-hand smoke).80 Later miscarriage may involve intrauterine death, premature delivery, or other events. Studies of women who work in microelectronic fabrication found rates of miscarriage to be 2.8 times higher than those women without such exposure.81 A growing body of epidemiologic literature associates air pollution with preterm birth and other adverse pregnancy outcomes, although it is not yet clear what aspect or constituent agent in air pollution may be causative.82

Organ development and the role of gene-environment interactions: Cardiogenesis

The heart is the first organ to develop during organogenesis, and its function is essential for embryonic survival. Cardiogenesis is complex and requires the assemblage and orientation of several functional components, processes that involve the carefully timed expression of growth factors. Such factors include the ubiquitous bone morphogenetic protein, which also plays a critical role in the development of the central nervous system,83 and the presence of nutrients (such as calcium and zinc) at critical times.84 Given that cardiovascular defects (CVDs) are among the most prominent terata in live born infants, and because they are often incompatible with postnatal survival, it is not surprising that considerable epidemiologic and experimental research has focused on environmental risks for CVDs. One of the major studies on inherited and acquired risk factors for CVDs was the Baltimore Washington Infant Study, which was conducted from 1981 to 1989 to enroll all live born infants with CVDs in the cities of Baltimore, Md, Washington, DC, suburban Maryland, and northern Virginia. Through careful diagnosis of specific defects and the collection of occupational and environmental histories, this study has revealed extraordinarily valuable information not only on environmental risks for specific CVDs but also on potential gene-environment interactions that may increase these risks. One such risk is a maternal history of organic solvent exposure.85 Several solvents, including ethanol, are associated with teratogenic outcomes in experimental animals86 and in the Baltimore Washington Infant Study cohort.85 We have examined the potential interactions between prenatal solvent exposure and genetic susceptibility. Specifically, we (and others) have hypothesized that susceptibility to solvent toxicity may be associated with polymorphisms in genes that encode enzyme proteins that are important in the activation or inactivation of solvents. A major set of
candidate genes in this regard are the glutathione-S-transferases (GSTs), which are important in phase 1 metabolism of many solvents. Using dried samples of neonatal blood spots that had been collected for diagnosis of phenylketonuria (Guthrie cards), Loffredo and Ewing demonstrated that DNA could be extracted and then used to test for polymorphisms in candidate genes. Examining interactions between several major CVDs, we have found that GST polymorphisms in black infants predispose such infants to an increased risk of atrial septal defect but not aortic valve stenosis or coarctation of the aorta in infants whose mothers reported solvent exposure during a critical period of exposure (Table III).

Figure 1  Schematic of the development of the relationship between the timing of an environmental insult (from preconception through birth) and “windows” of susceptibility by system.

Exposures later in organogenesis: Endocrine disruptors

Sublethal exposures later in organogenesis often are associated with functional rather than structural changes in the child. Endocrine disruptors are one set of compounds that have been proposed to induce these types of effects. Endocrine disruption is defined operationally as the interference with endogenous hormone function through several mechanisms, which include metabolic interruption, alterations in circulating hormone and prohormone levels, and binding of xenobiotics to hormone receptors. Exposures to endocrine-disrupting chemicals (EDCs) have been associated with significant adverse effects in both male and female animals, including laboratory rodents and wildlife population. In utero exposures have been reported to impact the development of the offspring’s reproductive and nervous system specifically. One chemical for which there are both experimental and clinical data is diethylstilbestrol, a potent synthetic estrogen and in many ways the paradigm EDC. The administration of diethylstilbestrol to pregnant women induced structural abnormalities in the reproductive system of both male and female fetuses. Prenatally exposed “diethylstilbes-
trol daughters’ experienced, as young women, an increased risk of infertility because of uterine and tubal problems and increased risks of vaginal adenocarcinomas. The dysmorphogenesis of the genitourinary system was first diagnosed when these “diethylstilbestrol daughters” found themselves unable to bear children; on examination, it was discovered that alterations in the entire structure of the vagina and uterus prevented successful pregnancy.

Several other estrogenic EDCs have been demonstrated to cause genitourinary dysmorphogenesis in animals. We have studied the effects of prenatal exposures of 2 potent estrogenic chemicals, 2,3,7,8-tetrachlorodibenzodioxin (TCDD) and chlordecone, on the development of the female reproductive tract in rats.95-97 TCDD exposures to pregnant rats in the later stages of gestation resulted in significant alterations in the perinatal program of uterine morphogenesis (Figure 2). These estrogenic chemicals inhibit apoptotic events that guide the normal regression of the Wolffian ducts in the female, which result in the continued presence of Wolffian remnants and interfere with the structural development of the mature genitourinary system.97 In rodents, the most striking evidence of this dysmorphogenesis in rodents is the appearance of a vaginal web, which is a tissue that partially occludes the vaginal opening (first reported by Gray and Ostby98). Other structural defects are observed in the clitoris.

Another target organ for endocrinologic effects of prenatal exposures to EDCs is the central nervous system. This information comes from experimental studies, because access to brain structure is not possible in human populations. Exposure to several EDCs, including diethylstilbestrol, have been associated with alterations in brain morphologic condition in rats, specifically in those hypothalamic regions that are organized by endogenous sex hormones in utero (Figure 3).95 At present there is no epidemiologic evidence to accept or reject the hypothesis that similar outcomes of central nervous system or genitourinary dysmorphogenesis may occur in humans who are exposed in utero to these chemicals. A suggestive correlate in humans is the effect of PCBs and dioxins on sex-typic play behavior in young children, which was reported in the prospective cohort study being carried out in the Netherlands.99

Reports from the PCB-exposed cohorts in Taiwan are suggestive of continuing problems in menstruation and other reproductive problems in young women, but no frank teratology similar to the events described in rodents has been found. In a recent update of the population that was exposed to TCDD in Seveso, Italy, menstrual irregularities and other problems were reported by women who were exposed while still menopausal in 1976.101 In boys, hypospadias have been associated with exposures to EDCs, but only in ecologic studies where specific exposures have not been ascertained.28 Anecdotal evidence has been reported from Vietnam, where some populations probably were exposed heavily to dioxins in Agent Orange.102 Reductions in the age of menarche have been described in human cohorts in which chemical exposures were suspected, but not identified.103 The importance of understanding the human relevance of these experimental studies is a motivating factor for the proposed National Children’s Longitudinal Study.25

### Table III: Gene Environment Interactions between maternal solvent exposure risks of cardiovascular malformations by infant genotype (glutathione-S-transferase theta)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n)</th>
<th>Control subjects (n)</th>
<th>Crude odds ratio</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed, theta (+)</td>
<td>32</td>
<td>111</td>
<td>1.0</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Unexposed, theta (0)</td>
<td>8</td>
<td>53</td>
<td>0.5</td>
<td>0.5</td>
<td>0.2-1.3</td>
</tr>
<tr>
<td>Exposed, theta (+)</td>
<td>5</td>
<td>2</td>
<td>8.7</td>
<td>23.2</td>
<td>3.7-143.6</td>
</tr>
<tr>
<td>Exposed, theta (0)</td>
<td>1</td>
<td>6</td>
<td>0.6</td>
<td>0.4</td>
<td>0.1-3.7</td>
</tr>
<tr>
<td>Black infants*</td>
<td>46</td>
<td>172</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A plus (+) indicates that an allele for the gene was present; a zero (0) indicates that no alleles were present.

*There were no white infants with the GST theta 0 genotype.

Mechanisms of action of environmental agents affecting pregnancy

There are many mechanisms by which environmental agents can affect pregnancy (including fertility and the in utero development of the next generation of women). The endocrine disruptors illustrate the importance of endocrinologic function for fertility, maintenance of pregnancy, and development of the reproductive system in utero and postnataally. The effects of solvents on teratogenesis during early embryo development demonstrate the potential for chemicals to interact with fundamental events in the early developmental program (such as signal transduction that involves the retinoic acid pathway). The bone morphogenetic proteins are another major group of molecular signals that are involved in organogenesis and can be affected by PCBs. The influence of pregnancy itself on the toxicity of certain chemicals is demonstrated by the ability of chemicals to be mobilized from maternal
stores and transferred across the placenta to the embryo and lactating infant and the increases in circulating levels of these chemicals as they move from maternal body stores to the fetus or breast milk.

One mechanism that has received little attention in reproductive toxicologic research is genomic imprinting. *Genomic imprinting* is defined as a mechanism that causes differential expression of parental alleles, which results from epigenetic modifications of genes in the germ line and embryo. Understanding the role of the differential expression of parental alleles in the offspring during development has significantly influenced our views of the potential for parent-specific exposure (of both male and female exposure) to affect both pregnancy and offspring development. Early events in pregnancy, which include communications between the trophoblast and the uterus and growth and placentation, are influenced highly by genes that now are known to be imprinted. These epigenetic determinants were thought to be inherited, but it is now understood that reprogramming of genomic imprinting and monoallelic expression can occur as a consequence of changes in the embryonic environment. For example, it is now accepted that genetic imprints can be altered during the in vitro culture of preimplantation embryos and that these modifications can result in increased risks of diseases that are associated with altered genetic imprinting (such as Beckwith-Wiedemann or Angelman syndromes, which have been reported to be increased in children who were delivered through assisted reproductive technology). These 2 syndromes are imprinting disorders that are associated with alterations in methylation of maternal alleles (H19 and IGF2R). Restrictions on dietary methionine in rats and mice also appear to influence the expression of imprinted genes by affecting methylation. These new data on the plasticity of imprinting suggest novel mechanisms for parental-specific impacts of environmental exposures on both pregnancy and offspring development. We currently are exploring these mechanisms in studies to identify mechanisms for the observations that paternal lead exposure can affect early gene expression in the 2-cell embryo and later neuronal development and behavior.

### Research needs

There are several research needs that are of great importance in the improvement of our knowledge of preventable risks to pregnancy and pregnant women. First, there is a need to examine human populations for evidence of the types of reproductive toxicity that have been described in animals (such as the dysmorphogenic effects of certain endocrine-disrupting chemicals on the development and later function of the female genitourinary tract). Second, there is an urgent need to “raise the consciousness” of researchers who are studying women’s health. Much more attention should be given to environmental and occupational risk factors for women. This situation is urgent; in the Women’s Health Initiative (the $600 million study of risks for osteoporosis, breast cancer, and other major illnesses in women),

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**Figure 2** Effects of TCDD on vaginal morphogenesis of the rat at gestational day 19. Female rats were treated once on gestational day 15 with 1 mg/kg TCDD. Note the altered vaginal structure, which results from persistent Wolffian duct remnants. (From Dienhart MK, Sommer RJ, Peterson RE, Hirshfield AN, Silbergeld EK. Gestational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin induces developmental defects in the rat vagina. Toxicol Sci 2000;56:141-9. With permission.)

**Figure 3** Effects of prenatal exposure to the highly estrogenic pesticide chlordan on the size of the sexually dimorphic nucleus (SDN) in female and male rats. In female rats, in utero exposure results in “masculinization” of the central nervous system, which is demonstrated by increased SDN volume. Note that control males normally have larger SDNs as compared with normal female rats (solid black bars). (From Laessig S. Developmental and behavioral neurotoxicity of endocrine disrupting chemicals. Baltimore [MD]: University of Maryland; 2000. With permission.)

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there was no effort made to obtain any information on women’s occupational exposures,\textsuperscript{56} which is carried out routinely in comparable epidemiologic studies of men. Third, more studies are needed on gene-environment interactions that are relevant to reproductive and developmental outcomes; much of this field of molecular epidemiology is still focused on cancer as an outcome. Similar to our study of solvents and GST polymorphisms, such studies may reveal other undetected risk factors for adverse pregnancy outcomes. Many of the questions that are raised in these studies may be answered at least in part through the proposed Children’s Longitudinal Health Study. This prospective long-term cohort study is designed to identify preventable factors for major childhood illnesses and disability, which include diabetes mellitus, behavioral disorders, asthma, and obesity. Careful design to identify environmental risk factors will greatly expand our knowledge for subsequent hypothesis testing.

In terms of basic research, advances in developmental biology have identified several key events that may be influenced by exogenous exposures. The role of highly conserved genes (such as retinoic acid receptors) and bone morphogenetic protein (bone morphogenetic protein) in tissue-specific developmental programs in the heart and central nervous system, for example, can assist in the use of molecular models for the identification and study of potential reproductive toxicants. The exciting area of genomic imprinting may provide mechanisms for designing further studies to examine associations between sex-specific (particularly paternal) exposures and adverse outcomes.

In summary, as pregnancy becomes more of a planned and chosen event in the lives of human families, the need to ensure optimal outcomes is heightened. Genetics alone greatly influence reproduction and development outcomes, but as with most human conditions, the genetic-environmental interaction is what determines both a healthy or adverse outcome.

References

Neighborhood context and reproductive health

Jennifer F. Culhane, PhD, MPH,a,* Irma T. Elo, PhD, MPA

Department of Obstetrics and Gynecology, Drexel University College of Medicine, Philadelphia, Pa,a and Department of Sociology, University of Pennsylvania, Philadelphia, Pa

KEY WORDS
Race
Reproductive health
Birth outcome
Neighborhood context

Racial and social class differences in rates of preterm birth and other adverse outcomes are among the most widely recognized and least well-understood phenomena in the study of reproductive health. Individual-level characteristics have failed to account for such gradients. Recently, researchers have begun to argue that health in general and reproductive outcomes specifically are rooted in social inequalities. One area of such inequality may be residential segregation and the associated race/ethnic differences in exposure to adverse neighborhood conditions. We review the empiric data that examine the association between neighborhood conditions and reproductive health. We also review the major challenges that researchers face when trying to incorporate neighborhood-level variables into studies of health outcomes. Our goal is to stimulate further research that simultaneously considers social, economic, and biologic determinants of reproductive health.

Racial and social class differences in rates of preterm birth (PTB) and other adverse outcomes are among the most widely recognized and least well-understood phenomena in the study of reproductive health. Black infants are twice as likely as white infants to be born low birth weight and 3 times as likely to be very low birth weight. Similarly, black women are twice as likely as white women to deliver before term, and this gap has been remarkably constant over the past 40 years.1-3 These racial disparities in birth outcomes are also largely responsible for the >2-fold excess in infant mortality rates among black infants.4 It is also well known that lower class women, independent of their race/ethnicity, have about a two-fold greater risk of preterm delivery compared with women in higher social classes.5 Yet, despite disparities in socioeconomic status between black and white women, socioeconomic status has failed to account for the entire racial gap.6 It further appears that benefits of income and education are not conferred equally to black and white women. Infants who are born to college-educated black women are at a much greater risk of PTB,5 low birth weight,7 and infant death,8 compared with infants born to college-educated white women.

In addition, other individual-level attributes (such as health behaviors and psychosocial characteristics) have not fully explained either the racial difference or the social class gradient in reproductive outcomes.6,9 In recent years, the failure of individual-level characteristics to account fully for these differentials has focused renewed attention on the possible role of the broader social context, which includes neighborhood conditions, in producing adverse birth outcomes.10 We review potential mechanisms through which neighborhood context may influence reproductive outcomes, including plausible
biologic mechanisms linking, neighborhood context to PTB. In addition, we discuss some of the theoretic and methodologic challenges in carrying out these types of studies. Our goal is to stimulate further research in this area and to draw attention to the importance of linking broad social and economic contexts with biologic mechanisms in future studies of reproductive health outcomes.

Conceptual framework

Neighborhood context

It has been suggested that the identification of plausible mechanisms through which neighborhood context influences health outcomes is perhaps the most pressing issue in the advancement of our understanding of how residential context translates into either good or bad health. In the Figure, drawing on previous studies, we outline a conceptual framework that links neighborhood context to adverse reproductive events highlighting important intervening variables along this pathway. In this model, neighborhood conditions that are hypothesized to influence health, either directly or indirectly, are features of the neighborhood’s social environment, service environment, and physical characteristics. Social environment refers to the level of neighborhood cohesion or disorganization, norms of reciprocity, civic participation, crime, socioeconomic composition, residential stability, and related attributes. These characteristics are hypothesized to influence health outcomes through a number of potential pathways that include availability of social support, adaptation of coping strategies, and exposure to chronic stress. Previous studies have found that women who live in violent, crime-ridden, and physically decayed neighborhoods are more likely to experience pregnancy complications and adverse birth outcomes, after adjustment for a range of individual-level sociodemographic attributes and health behaviors. In addition, studies have further pointed to the potential importance of neighborhood-level social relations for reproductive health.

Characteristics of community service environment reflect the availability of goods and services, such as access to quality health care, grocery stores, recreational facilities, and police and fire protection. The availability of such services is likely to be affected by the degree of political organization that influences the residents’ ability to demand public services and recruit private service providers to their neighborhoods. Poor public and private services may have a direct and indirect impact on an individual’s health by making residents more susceptible to intentional and unintentional injuries; by limiting access to quality health care, healthy foods, and recreational opportunities; and by increasing crime rates. Finally, the quality of the physical environment, which includes exposure to toxicants, noise and air pollution, and quality of the housing stock and public space, could have direct effects on health. The concentration of adverse neighborhood conditions along all 3 dimensions discussed above are often closely tied to the clustering of socioeconomic disadvantage. Thus, not surprisingly, a number of studies have documented a significant association between neighborhood-level socioeconomic disadvantage and birth outcomes.
In addition, living in racially or ethnically segregated neighborhoods may influence health over and above individual-level attributes.\textsuperscript{16,28,29} Residential segregation had led to race/ethnic differences in exposure to adverse neighborhood conditions, differences that are most pronounced between white and black women. Black women are more likely than white women to live in neighborhoods with poor municipal services, limited access to quality health care, high rates of crime and violence, and poor quality housing.\textsuperscript{30,31} Closely associated with residential segregation are other forms of racial discrimination with potential adverse health consequences, including adverse birth outcomes.\textsuperscript{32-36} For example, in previous studies, a positive association between black/white segregation and infant mortality rates has been documented for black infants.\textsuperscript{37,38} At the same time, for other ethnic groups, living in ethnic enclaves may confer health advantages. For example, the case has been made that Mexican women, who live in predominantly Mexican immigrant neighborhoods, deliver babies with higher birth weight.\textsuperscript{16}

**Individual-level characteristics**

Neighborhood characteristics may exert their influence on reproductive outcomes indirectly by patterning individual-level economic opportunities and health behaviors. For example, neighborhood-level opportunity structure may restrict or facilitate access to schooling, training programs, and employment opportunities and thus influence reproductive outcomes through a woman’s attained socioeconomic status.\textsuperscript{13,39} Thus, socioeconomic status disparities in birth outcomes may originate in part in neighborhood context that shape individuals’ life chances.

Furthermore, social characteristics of neighborhoods, perhaps through shared cultural norms and values, may well influence health behaviors associated with adverse reproductive outcomes. For example, individual-level smoking patterns,\textsuperscript{40,41} alcohol consumption, and dietary practices,\textsuperscript{42-46} which seem particularly relevant to this discussion, have been significantly associated with area-level deprivation when controlling for individual attributes. We suggest that, in addition to health behaviors, adverse conditions (such as high crime rates, housing abandonment, and even noise pollution) may act as either acute or chronic stressors that exert their influence through stress physiologic factors and are thus potential intervening mechanisms between neighborhood context and reproductive health. Geronimus,\textsuperscript{47} for example, has argued forcefully that long-term exposure to socioeconomic disadvantage, which includes residence in socioeconomically disadvantaged neighborhoods, is detrimental for maternal reproductive health and is one of the factors that contribute to more adverse birth outcomes among black women rather than white women.

Thus, we have also included exposure to acute and chronic stress as one of the hypothesized pathways through which neighborhood context may affect birth outcomes. At the individual level, a growing body of empirical evidence based on methodologically rigorous studies of pregnant women of different ethnic, socioeconomic, and cultural backgrounds, supports the premise that mothers who experience high levels of psychologic or social stress during pregnancy are at significantly increased risk for PTB (relative risk, 1.5-2.0), even after an adjustment is made for other biomedical, sociodemographic, and behavioral risk factors.\textsuperscript{48,49} In addition, we found that adverse neighborhood conditions, such as crime, homelessness, and tax delinquency, were associated significantly with risk of urogenital tract infection, which is one of the leading causes of PTB,\textsuperscript{50,51} even after an adjustment is made for individual-level risk factors.\textsuperscript{52}

Finally, we should note that neighborhood context and individual characteristics may interact such that individual characteristics may exert greater influence in certain neighborhoods or that the effects of neighborhood context are more pronounced for subgroups of women who are stratified by socioeconomic status, race/ethnicity, or other individual attributes. For example, a recent study in Chicago found that high perceived levels of neighborhood support were associated positively with birth weight only for white infants and that a significant negative association between birth weight and neighborhood-level economic disadvantage was documented for black infants.\textsuperscript{15} This association remained significant even after an adjustment for maternal characteristics and other neighborhood conditions.\textsuperscript{15} O’Campo et al\textsuperscript{11,24} found that the early initiation of prenatal care did not have the same beneficial effect for women who lived in disadvantaged neighborhoods in Baltimore, Md, which raised the possibility that prenatal care in deprived settings is unable to address various risks that are associated with adverse birth outcomes.

**Biological mechanisms**

As noted earlier, neighborhood conditions such as high rates of crime and abandoned and dilapidated housing are conceptualized as stressful exposures and thus are hypothesized to have similar physiologic consequences as do more traditional individual-level experiences, such as negative life events. Stress, both at the individual and neighborhood level, may affect PTB through 2 major physiologic pathways. The first is a direct neuroendocrine pathway that ultimately results in premature and/or greater activation of the maternal-placental-fetal endocrine systems that promote parturition. The second potential mechanism is an immune/inflammatory pathway wherein maternal stress may modulate characteristics of systemic and local immunity to increase
susceptibility to infection or the proinflammatory response to an existing infection.\textsuperscript{52-54}

The plausibility of the direct neuroendocrine and the neuroendocrine-immune interaction pathways suggests that stressful exposures may have physiologic consequences over and above their possible influence on health-related behaviors. As evidence accumulates that individual-level stressful exposures can “get under the skin,” it is not hard to imagine that dangerous and rundown neighborhoods may exert a similar effect. It is therefore possible that neighborhoods can influence health outcomes through direct physiologic dysregulation.

**Methodologic considerations**

Although there is a growing body of research on the effects of neighborhood conditions on reproductive and other health outcomes, the study of whether and how community conditions influence health faces a number of theoretic and methodologic challenges.

**How should neighborhoods be defined?**

Most studies that have examined the effects of neighborhood conditions on health outcomes have used administrative or political boundaries to characterize neighborhoods. In the United States, studies of reproductive and other health outcomes commonly have defined neighborhoods with the use of US census tracts.\textsuperscript{17,24,55,56} Alternatively, some studies have used census block groups\textsuperscript{19,25} or alternative neighborhood boundaries.\textsuperscript{15,16} The choice of census-based administrative units has been driven largely by convenience and the availability of decennial census data for a wide range of population and housing characteristics. However, these neighborhood units may provide only a rough measure of neighborhood context and therefore lead to incorrect specification of the effects of neighborhood characteristics.\textsuperscript{12,57} The assignment of an erroneous value for exposure to a neighborhood condition because of an arbitrary geographic boundary is known as aggregation or zone effect, which stems from the fact that all residents in a given neighborhood are assigned the same exposure.\textsuperscript{58-60} Census tracts, for example, were designed originally to encompass areas with a similar population size and similar socioeconomic, housing, and demographic characteristics.\textsuperscript{61} There can be considerable variation in characteristics within census tracts, however, and individuals who reside in the same tract may experience very different “neighborhood” conditions. The same may be true for the smaller level of census aggregation known as block groups, which are subunits within census tracts, although these areas are likely to be more homogenous in their characteristics. Nevertheless, recent study that examined the association between census tract and block group level measures of socioeconomic status and rates of low birth weight, childhood lead poisoning, and mortality rates concluded that census tract and block group level measures provided similar results. The same socioeconomic measures and health outcomes that were based on zip code areas, however, were found to be less effective.\textsuperscript{61-63} To overcome problems that are posed by the use of conventional census geography, 2 recent studies have modeled neighborhood effects on birth weight using boundaries that were delineated on the basis of homogenous neighborhood clusters and knowledge of traditional Chicago neighborhoods,\textsuperscript{15,16} which is an approach that merits replication in other settings. Yet, surprisingly few studies have examined whether the way in which the neighborhood is defined has a substantive impact on findings of neighborhood effects on health outcomes.

An additional challenge in the examination of the effects of neighborhood conditions on reproductive and other health outcomes is the choice of an appropriate scale for the exposure of interest.\textsuperscript{58-60,64} The imposition of a fixed spatial scale (such as census block groups or tracts) for all types of neighborhood exposures may not be appropriate. For example, if nearby conditions (such as the concentration of abandoned building or broken windows\textsuperscript{65}) is associated with health outcomes, how near or far do the abandoned buildings or broken windows need to be? It also is likely that appropriate neighborhood boundaries will vary for different neighborhood conditions (such as availability of health care services and retail stores vs exposure to violent crime). Thus, careful thought should be given to the spatial scale of neighborhood boundaries for alternative measures of neighborhood context.\textsuperscript{11} Furthermore, higher levels of aggregation (such as states, counties, and cities or metropolitan areas) may be relevant and suggest the need to consider multiple levels of community context.

In addition, the literature on neighborhood effects emphasizes another related analytic issue, namely spatial autocorrelation, which has not been considered in most empiric studies of neighborhood effects on birth outcomes with the exception of Morenoff’s\textsuperscript{16} study of birth weight in Chicago. Spatial autocorrelation is present when nearby or adjacent neighborhoods have similar outcomes (often referred to as spatial dependence), such as PTB rates, that are not accounted for after an adjustment is made for neighborhood characteristics (such as high crime rates or high rates of neighborhood poverty).\textsuperscript{58,66,67} Although adjustment for neighborhood characteristics can reduce the impact of spatial autocorrelation by capturing some of this spatial dependence, often significant unobserved spatial dependencies may remain that can generate correlations among outcome variables in adjacent neighborhoods. That spatial autocorrelation can be significant in the analyses of reproductive outcomes in urban areas, even when a host of individual-level and neighborhood-level characteristics are included in the analysis is illustrated.
by Morenoff. The results from this study show that social environment beyond the woman’s own neighborhood (ie, in adjacent neighborhoods) exerted an influence on birth weight, suggesting that such interdependence should be considered in analyses of neighborhood effects at least in urban contexts. Another consideration, although not directly related to what definition of neighborhood should be considered, relates to the potential bias in estimates of neighborhood effects when residential choice itself is not considered. Because individuals are not assigned randomly to neighborhoods and unobserved characteristics that influence the choice of residence are also likely to influence health outcomes, the estimation of causal neighborhood effects is problematic with observational data. The collection of longitudinal data and the modeling of residential choice may help shed light on some of these potential biases and should be encouraged.

How should neighborhood context be measured?

There are 2 types of data that can be used to characterize neighborhoods: (1) aggregate or derived variables that are created from individual-level characteristics of neighborhood residents and (2) structural or integral variables that do not have equivalent measures at the individual level (such as housing quality, the availability of goods and services, air pollution, the presence of toxic waste sites). Most studies have used aggregate-level variables that were created from individual-level data that usually were represented as means, medians, and distributions of such characteristics as household income, poverty, public assistance use, educational attainment, unemployment rates, and race/ethnic composition of neighborhoods. It is often hypothesized that aggregates of individual-level characteristics serve as proxies for structural variables such as service availability, housing quality, and levels of crime and violence. Relatively few studies have included the latter type of community-level measures such as crime rates, housing quality, and the presence of commercial establishments. The relative absence of structural or integral variables probably reflects the limited availability of these types of data and is a limitation in this field.

Researchers face several challenges in characterizing neighborhood context using readily available derived data. First, these data provide an incomplete depiction of actual neighborhood conditions. In other words, not all neighborhoods that are characterized as poor and disadvantaged based on census variables are actually alike. Rates of crime and violence, the quality of social networks, public and private services, and other relevant neighborhood characteristics may vary substantially across what appear to be similarly disadvantaged areas. Data to develop measures of neighborhood context that could differentiate between what appear to be homogeneously socioeconomically disadvantaged neighborhoods are needed. For example, recent studies that have incorporated measures of social support and violent crime have demonstrated the usefulness of the inclusion of a more varied set of neighborhood measures in the analyses of reproductive outcomes. Potentially useful, but largely untapped, sources of neighborhood-level data are administrative records that are maintained by local governments and institutions. In addition, community surveys that solicit information about residents’ perceptions of neighborhood context are potentially useful data for understanding neighborhood-level dynamics. An additional source of information is observational data that may be used to capture neighborhood characteristics that are otherwise unavailable and that can provide “objective” measures of neighborhood context and that are independent of the perceptions of neighborhood residents. An example of these approaches is the Project on Human Development in Chicago neighborhoods, which solicited information on neighborhood quality from a survey of area residents and objective indicators of neighborhood-level social and physical disorder.

The second challenge facing researchers is an analytic problem caused by the high correlation among numerous neighborhood-level variables (such as poverty, low levels of education, poor housing quality). One possible solution is to develop indices of related neighborhood-level conditions, although such indices obscure the discrete effect of each distinct component. In addition, the ability to estimate the independent contribution of neighborhood context to health outcomes requires an adequate adjustment for individual-level characteristics. Without individual-level data, contextual-level effects may reflect unmeasured individual-level differences rather than independent effects of neighborhood context, although careful thought should be given to which individual-level factors are likely to act as confounders and which factors are considered intervening variables.

Finally, to date, the emphasis in this field has been to study the association between a woman’s current neighborhood context and her reproductive outcomes. Possibly, reproductive disadvantage is established early in the life course; therefore, a woman’s neighborhood exposures in her early childhood or even during her own gestation may be as important in shaping her reproductive outcomes as her current neighborhood exposures. This emphasis undoubtedly stems from the cross-sectional nature of data that are used in most studies and the notion that current neighborhood conditions are a fairly good proxy for past conditions. A recent study of past and present neighborhood conditions on mental health status challenges this assumption by empirically demonstrating that a lagged effect of childhood neighborhood conditions is a better predictor of mental health status in early
adulthood, compared with current neighborhood conditions. The need for a life course perspective has also been recognized in the study of physical health outcomes.

Comment

The notion that community-level conditions can produce profound effects on host susceptibility to disease derives in part from the long-standing existence of strong social class and race/ethnic gradients in health and death and the inability of individual-level characteristics to account for such gradients. The emphasis on community context has a long history in public health. Initially, the field of public health was dominated by concerns with neighborhood variation in health outcomes and associations between community conditions and infectious diseases. As chronic disease became the major cause of morbidity and death, public health focus shifted from the community to the individual. It is only relatively recently that neighborhood context has again begun to play an increasingly important role in epidemiologic theories of health. The question of whether neighborhood context influences health outcomes over and above individual characteristics has also received heightened attention in the sociologic literature on health and death in recent years. Advances in statistical techniques that facilitate the modeling of multilevel influences and the growing interest in the use of geographic information systems have also made analyses of community-level variation and influences on health outcomes more feasible.

Clearly, additional work is required to investigate optimal ways to conceptualize neighborhood and to explore the extent to which the association between neighborhood conditions and health outcomes vary depending on how neighborhood boundaries are defined. Despite their convenience, political and administrative units may not be the most appropriate way to delineate neighborhood boundaries. Furthermore, it may well be that different neighborhood exposures exert their influence on health at varying levels of aggregation. Larger catchment areas, for example, may be appropriate for the measurement of availability of goods and services (such as health care facilities, recreational opportunities and grocery stores); smaller geographic units may be more appropriate for the assessment of the quality of housing stock, crime, and social characteristics of neighborhoods. Thus, it may be important to incorporate multiple levels of influence simultaneously, depending on the research question and the theoretic framework that is used to guide the analysis. Studies that pay explicit attention to these issues and other methodologic considerations are needed to advance our understanding of the potential influences neighborhood context exert on health outcomes.

References

Psychosocial stress and neuroendocrine mechanisms in preterm delivery

Janet W. Rich-Edwards, ScD,* Tarayn A. Grizzard, BS

Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Mass

KEY WORDS
Preterm delivery
Psychosocial stress
Weathering
Race

This review focuses on the contribution of psychosocial stress to the racial/ethnic disparities in preterm delivery in the United States and addresses the subset of psychosocial stressors that are disproportionately prevalent among minority women. We argue that chronic exposure to poverty, racism, and insecure neighborhoods may condition stress responses and physiologic changes in ways that increase the risk of preterm delivery. Cumulative stressors may impact pregnancy outcomes through several intersecting pathways, which include neuroendocrine, behavioral, immune, and vascular mechanisms. Many of these pathways also lead to chronic disease. It may be useful to consider preterm delivery as a chronic disease with roots in childhood, adolescence, and early adulthood. Like other physiologic systems, the female reproductive axis may be vulnerable to the physiologic “wear and tear” of cumulative stress, which results in preterm delivery.

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Although medical advances over the past 50 years have reduced the incidence of infant mortality in the United States, they have failed to resolve the disparities that are seen in rates of white and black infant mortality rates. The infant mortality ratio for black infants is nearly twice that of white infants and is driven by disparities in rates of preterm delivery, the largest single cause of neonatal death.1

This review will focus on the possible contribution of psychosocial stress to the racial/ethnic disparities in preterm delivery in the United States, with a focus on potential neuroendocrine mediators. Stress, as generically used, has many meanings that range from environmental and pathophysiologic stressors to individual psychologic and physiologic responses to those stressors. We will address only a subset of environmental stressors, known broadly as psychosocial stressors, with a narrow focus on stressors that are particularly relevant to minority women. There are several candidate pathways by which psychosocial stress might impact pregnancy outcomes2; these intersecting pathways include behavioral, immune, and vascular mechanisms and neuroendocrine pathways.

Psychosocial stressors and pregnancy outcomes

Many attempts have been made to explain the racial/ethnic gap in preterm rates as a function of social and economic disparities in income, maternal education, and marital status.3 Recently, investigators have also...
examined such factors as social support, experiences of racism, and neighborhood violence. Many of these stressors are chronic exposures that long predate the pregnancy. First, we argue that chronic cumulative stress impacts on pregnancy outcomes before we turn to some specific stressors of interest.

**Weathering, race, and reproduction**

A series of studies that used birth registry data from Michigan, New York City, and Chicago have demonstrated repeatedly that the risk of delivering a low birth weight infant rises more steeply with maternal age for black mothers compared with white mothers. This pattern is also evident in national preterm delivery statistics that demonstrate that the lowest risk age for preterm delivery is 30 to 34 years for non-Latina white mothers, compared with 25 to 29 years for Latina mothers and non-Latina black mothers (Figure). It is as if the age-associated increase in poor pregnancy outcome has been shifted to the left among minority women and is steepest among black women.

Geronimus coined the phrase *weathering hypothesis* to describe this seeming phenomenon of premature aging among black women, which she attributed to experiences of poverty and discrimination. Indeed, in the Chicago analysis, and to a lesser extent in the New York and Michigan analyses, the steep age-related increase in the risk of poor pregnancy outcomes among black mothers was explained by social and economic risk factors and particularly by the interaction of social and economic risk factors with maternal age. In other words, older mothers at social and material disadvantage were at especially high risk of poor pregnancy outcome, regardless of race/ethnicity. The fact that social and economic risk factors appear to have a greater impact among older mothers may reflect a cumulative impact on a woman’s reproductive health of long-term exposure to stressful social and economic environments. According to this interpretation, the accumulating burdens of poverty and discrimination compromise a woman’s health and chances of being delivered of a healthy infant, even before she conceives the pregnancy.

However, cross-sectional data (such as these collected in Michigan, New York, and Chicago) cannot establish whether women are weathered by low socioeconomic position. There are alternative interpretations that include social determinants of the age at which a woman bears her children and possible biologic interactions of low socioeconomic position with advanced maternal age. Future longitudinal studies may determine whether this high risk among older disadvantaged mothers indicates a cumulative, weathering exposure to hardship.

**Socioeconomic position**

Economic stresses like low household income and neighborhood poverty and related structural problems have been related to an increased risk of poor pregnancy outcomes in black women. However, the racial/ethnic disparity in pregnancy outcomes remains even after being controlled for maternal educational attainment and socioeconomic position, with college-educated black women experiencing greater rates of preterm labor than their college-educated white peers. Many studies
have demonstrated that socioeconomic position, as measured by standard measures of maternal education, household income, and use of public assistance, explains only a part of the disparity in pregnancy outcomes between black and white mothers.\textsuperscript{14,16-19} As discussed by Hogue in this supplement, this failure to explain racial disparities may reflect the poverty of our socioeconomic measures, which do not capture differences in individual wealth, financial security, and extent of economic obligations to family and community. Furthermore, these measures do not capture socioeconomic circumstances in childhood, which may be at least as important to pregnancy outcomes as socioeconomic position during pregnancy.\textsuperscript{20-22} Thus, it may yet prove that socioeconomic factors explain much more of the racial/ethnic disparities than currently appreciated.

Racism

It has also been proposed that experiences of racism constitute a chronic stressor that is experienced by black women across the socioeconomic spectrum.\textsuperscript{3,23,24} Black women are 4 times as likely as other minority groups to report daily or weekly incidents of racism.\textsuperscript{25} Several studies indicate stronger blood pressure and stress hormone response to experimental racially charged situations among black women or among black women who report everyday discrimination.\textsuperscript{26-28} In a case-control study by Collins et al,\textsuperscript{7} low income black women who were delivered of infants who weighed <1500 g were twice as likely to report incidents of racism during their pregnancies compared with women who were delivered of a normal-weight infant with complications. However, an earlier, smaller study found no associations between self-reported experiences of racism and offspring birth weight.\textsuperscript{29} More recently, reported findings from the Black Women’s Health Study are equivocal with regard to an impact of individually directed racism on the risk of preterm birth.\textsuperscript{30} Although modest increases in the risk of preterm birth were reported for some instances of perceived racism (specifically, racism “on the job” and people acting “afraid” of the participant) particularly among women with lower levels of education, other measures had no association with pregnancy outcome.\textsuperscript{30}

Neighborhood context

Ecologic stresses (such as disorderly or violent neighborhoods) may also be part of the cumulative stress that is associated with life as a black woman and have been associated with poor pregnancy outcomes. A study of women of low socioeconomic position who live in the most violent of Chicago’s South Side neighborhoods showed that these women had an increased rate of delivery of small for gestational age and very low birth weight infants compared with women of comparable socioeconomic standing living in the least violent neighborhoods.\textsuperscript{5} In another study, women who characterized their neighborhoods as “unsafe,” “violent,” and “unfriendly” also had an increased risk of being delivered of a very low birth weight infant, independent of other risk factors (such as smoking and substance abuse).\textsuperscript{4} Although such studies must be replicated, they are steps in “unpacking” the long-standing associations of low social position with health outcomes.

Chronic stress: Prepregnancy priming for preterm delivery?

Experiences of poverty, racism, and lack of neighborhood safety are likely to date back to a mother’s childhood, if not to previous generations. Such lifelong exposures may shape the reproductive health of girls and young women, thus “priming” the likelihood of poor pregnancy outcomes before the pregnancy is conceived. We can borrow paradigms from chronic disease epidemiologic conditions (such as the concept of allostatic load\textsuperscript{31}) to understand the cumulative impact of enduring stress on health. Indeed, it may be helpful to consider poor pregnancy outcomes as part of chronic disease processes. Just as diabetes mellitus and immune disorders have been associated with the physiologic “wear and tear” of prolonged stress response, so the female reproductive axis may be vulnerable to chronic stress with poor pregnancy outcomes as a result.

Preterm and low birth weight as chronic disease

Maternal endocrine and immune systems that are shaped by chronic stressors before conception may create particular vulnerabilities to pregnancy complications and preterm delivery. To some extent, poor pregnancy outcomes are a manifestation of chronic disease processes that are already underway in young women. The physiologic stress of pregnancy often reveals latent tendencies toward future chronic disease. For example, preeclampsia and other hypertensive disorders predict later hypertension.\textsuperscript{32,33} Similarly, women with gestational diabetes mellitus are at considerably higher risk of the development of type 2 diabetes mellitus.\textsuperscript{34,35} Studies from Europe have demonstrated that the delivery of a preterm or low birth weight infant predicts a higher risk of future cardiovascular disease\textsuperscript{33,36,37} and, in some studies, breast cancer.\textsuperscript{38,39} It is plausible that the chronic psychosocial stressors that are responsible for weathering a woman’s endocrine, immune, and reproductive systems are manifest first as poor pregnancy outcomes and later as chronic disease. Poor pregnancy outcome may be a sides
Neuroendocrine pathways linking chronic stress and preterm delivery

There are numerous intersecting pathways—neural, endocrine, immune, vascular—through which an accumulating burden of psychosocial stressors might affect pregnancy outcome. We will build an argument that weathering by repeated stress may alter neuroendocrine mechanisms that are related to the risk of preterm delivery.

“Kindling” and stress response

The hypothalamic-adrenal-pituitary axis remains plastic throughout life and is molded and remodeled by environmental stressors. Experimental studies have shown that chronic stress can prime, or “kindle,” amygdalic and hippocampal reaction to novel stressors. In animal models, repeated stress up-regulates amygdalic corticotropin-releasing hormone (CRH) gene expression and elevates serum CRH levels, which creates a state of hypervigilance or “arousal pathology.” In humans, psychophysioligic studies have demonstrated exaggerated physiologic responses to novel stressors among women with high levels of chronic stress in their past. For example, women who were sexually abused as children have an exaggerated adrenocorticotropic hormone response to a public speaking task. Black women who report experiencing high levels of “everyday” racism have greater blood pressure reactivity to a public-speaking challenge. Studies such as these suggest that previous aversive conditioning by chronic stressors may condition or “kindle” future stress responses.

Does such “arousal pathology” affect pregnancy outcomes? The question is largely untested. However, one study reported strong negative correlations between maternal diastolic blood pressure response to an arithmetic test during pregnancy and the duration of pregnancy. Other studies have reported that maternal anxiety is associated with increased vascular resistance of the umbilical and uterine arteries, which are factors that are associated with fetal hypoxia and growth restriction. Thus, one pathway between maternal psychosocial stress and stress reactivity may lead through vascular responses to stress.

Placental CRH

It has also been suggested that maternal stress hormones may play a role in preterm delivery through their interaction with placental hormone production. The placenta produces prodigious amounts of CRH, which is up-regulated by both fetal and maternal cortisol. By mid gestation, CRH levels are correlated inversely with gestational length. Although it is not established whether CRH causes preterm delivery, the ability of CRH to stimulate cytokine release from decidua and amnion in vitro and its potentiating effect on oxytocin-stimulated myometrial contraction strongly suggest a direct causal role in triggering parturition. The role of other maternal stress hormones (such as adrenocorticotropic hormone) is also under investigation.

In vitro studies have shown that cultured placental cells increase CRH production in response to cortisol and catecholamines. This begs the question of whether maternal characteristics, which include maternal race/ethnicity, social position, and perceived stress, are related to CRH levels in maternal blood during pregnancy. A handful of studies have reported associations between maternal race/ethnicity and CRH levels. One study reported higher CRH levels among black, compared with white, mothers. In contrast, Holzman et al reported lower CRH levels among black mothers, although the association between CRH level and gestational length was stronger among black women than among white women. Two studies have reported lower CRH levels in Latina mothers than in white mothers. To our knowledge, only 2 studies have examined whether social position was associated with CRH levels. A US study reported an association between low family income and high maternal CRH, although a Danish study reported high CRH levels among women with low education or who received public assistance.

Other studies of CRH in pregnancy suggest that perceived stress impacts CRH levels during pregnancy. In a study by Hobel et al, self-reported maternal stress at 18 to 20 weeks of gestation predicted a rise in CRH levels at 28 to 30 weeks of gestation. In Los Angeles, CRH levels were elevated in patients who reported higher levels of stress/anxiety or who experienced “hassles” on the day of the study. However, findings are not unanimous; Petraglia et al found no associations of CRH and catecholamine levels with adverse life events, job strain, or lack of social support.

Neuroendocrine infection interactions

Infection and inflammation of the maternal genital tract are believed to account for 20% to 30% of preterm deliveries and a higher proportion of very preterm (<32 weeks of gestation) deliveries. Bacterial vaginosis, the most consistently associated infection with preterm labor, is more prevalent among black women. Even after being controlled for socioeconomic position, douching, and sexual practices, data show that black women have significantly increased rates of bacterial infection and inflammation of the maternal genital tract.
vaginosis compared with their white counterparts. It may be that factors in the environment of black women increase individual susceptibility and inflammatory reaction to infection; psychosocial stress is a prime candidate. Culhane showed that the higher rates of bacterial vaginosis in pregnant black women in Philadelphia could be explained partially by the greater psychosocial stress that was reported by these mothers. As in all survey-based studies of stress, imprecision in the measurement of perceived stress probably led to an underestimate of its impact. It may prove that psychosocial stress explains much of the black-white differential in bacterial vaginosis prevalence. Further investigation of the role of psychosocial stress and its mediators in the regulation of immune function in pregnancy is urgently needed.

Comment

Circumstantial evidence is building to suggest ways in which chronic stressors, which include poverty and racism, that are borne by many minority women may shape reproductive health and pregnancy outcomes. More research is needed to understand whether and how accumulating burdens of psychosocial stressors indeed “weather” women. Although studies are beginning to link specific chronic stressors (such as social or economic position) to perceived stress (such as perceived racism or anxiety) to physiologic stress responses (such as blood pressure or hormone reactivity), risk factors for preterm delivery (such as placental diseases or infection) and risk of preterm delivery, these studies are few, small, and sometimes contradictory. Although this pioneering work suggests much, it still has much to prove. Future research will continue to pursue the impact of living in the United States as a woman of color on neuroendocrine function and the risk of preterm delivery.

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References

Biochemical markers for the prediction of preterm birth

Robert L. Goldenberg, MD, Alice R. Goepfert, MD, Patrick S. Ramsey, MD

The Center for Research in Women’s Health and the Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Ala

KEY WORDS
Preterm birth
Biologic fluid

The prediction of preterm birth may be important (1) to initiate risk specific treatment; (2) to define a population that is at risk in which to study a particular treatment; or (3) to better understand the pathways that lead to preterm birth. Biologic fluids that have been used as sources for tests include serum, plasma, amniotic fluid, urine, vaginal and cervical secretions, saliva, and even periodontal fluid. We discuss the types of substances that are found in body fluids (eg, organisms, cytokines, enzymes, hormones) that have been studied as predictors of preterm birth, the fluids in which they are found, and issues that are related to the timing of the test, the cost, and the ease of fluid collection and processing. We emphasize that a test for any of these substances should not be introduced into clinical practice until the use of the test, which is followed by an appropriate intervention, leads to a reduction in preterm birth.

Preterm birth is the event most responsible for poor pregnancy outcome in the United States and many other developed countries.1,2 It accounts for approximately 70% of all neonatal deaths and approximately one-half of the long-term neurologic disability.3 We will restrict our discussion to those preterm births that are defined as spontaneous (that is, those births which occur at <37 weeks of gestation after the spontaneous onset of labor or rupture of the fetal membranes). Births that follow a physician’s decision to deliver the fetus preterm because of maternal or fetal indications will not be considered.

The prediction of which pregnancies will end in preterm birth is a reasonable goal for several reasons.4-6 First, predicting which women might have a preterm delivery may allow us to initiate appropriate risk-specific treatment. Second, it may help us to define a population of women who are at risk so that we can study a particular treatment. Finally, being able to predict which women will have a subsequent preterm birth may allow us to gain important insights into the mechanisms or pathways that ultimately lead to a preterm birth.

The term marker is not well-defined. A marker for preterm birth could include any factor that predicts subsequent spontaneous preterm birth, including demographic factors, personal behaviors, physical characteristics, findings on a physical examination, a short cervical length by ultrasound examination, or measurement of a particular substance in a biologic fluid.4,6 We will focus only on markers that are found in biologic fluids.
Sources of biologic fluid

Biologic fluids that have been used as a source to define markers for preterm birth have included amniotic fluid, urine, cervical mucus, vaginal secretions, serum and/or plasma, and less obvious sources such as saliva and even fluid taken from the dental pockets of women with periodontal disease (crevicular fluid). The first decision to make in the study of a particular substance as a potential marker for preterm birth is whether it is biologically plausible that an increase or decrease in that particular substance in that particular fluid is likely to occur in women who are at risk for preterm delivery. Factors that should impact on whether a specific fluid should be chosen for study would also include the ease of obtaining that fluid, the cost of obtaining the fluid, and issues such as the risk to the mother or fetus. For example, fluids such as serum/plasma, urine, and saliva are relatively easy and inexpensive to collect and are obtainable at essentially no risk and with very limited discomfort for the patient. In contrast, the collection of fluid through ultrasound-guided amniocentesis requires an invasive, costly procedure that does impose some risks and discomfort for the patient.

One also must consider the indications for which the markers are being evaluated. For example, if the presence of the marker will enable us to elucidate a mechanism that could lead to preterm birth or an expensive and perhaps even somewhat risky procedure ultimately may be of value if it advances our understanding of the pathophysiologic condition. Alternatively, if the marker is being studied as a screening tool to identify a high-risk population for the implementation of a specific intervention, issues such as safety, ease of collection, and costs may be of greater concern. Examples of markers that are associated with preterm birth include various cytokines in periodontal (crevicular) fluid, cytokines and organisms such as Chlamydia that are found in urine samples, salivary estriol measurements, and a wide variety of organisms, cytokines, and other substances in amniotic fluid, serum, plasma, and cervicovaginal secretions. At times, the study of these biomarkers may provide information regarding both the pathophysiologic mechanisms that lead to preterm birth and their usefulness as a screening tool to identify women who are at high risk for subsequent preterm delivery. However, in general, we believe that studies of various markers of preterm birth would be more useful if the intended use of the particular biomarker was decided on before the initiation of the study.

Timing

The issue of timing in relationship to usefulness of biologic markers rarely has been considered in sufficient detail. Timing, for example, can be considered by the hours, days, weeks, or months before the preterm delivery. Timing can also be considered in relationship to the gestational age at the time that the sample is collected. For example, we have evaluated a number of markers (including alkaline phosphatase and ferritin) in serum in relationship to the gestational age at which they achieve maximum predictability. With both of those substances, plasma levels at <20 weeks of gestation were of little value in the prediction of a preterm birth, although samples that were obtained at 24 weeks of gestation were highly predictive of preterm birth. Similarly, fetal fibronectin, which is a powerful marker for subsequent preterm birth when measured at ≥24 weeks of gestation, has much less predictive value when measured at earlier gestational ages. It is crucial therefore to understand at which gestational ages a marker may be useful for the prediction of preterm birth.

An understanding of when a marker turns positive in relationship to the preterm birth is also important. For example, we have studied matrix metalloproteinase-9 as a predictor of preterm labor or preterm premature rupture of membranes (PPROM). This particular marker, when measured in serum, turned positive approximately 24 hours before the initiation of labor or PPROM. Although telling us something about the pathway that leads to prematurity, this particular marker, when used clinically, will almost certainly not be a valuable test because there is so little time between the test turning positive and the beginning of labor or PPROM to initiate an intervention. Bacterial vaginosis, when considered as a marker for a subsequent preterm birth, is interesting not so much because it is a strong predictor of prematurity (relative risk of only 1.5-2.0) but because it is present sufficiently early both in gestational age and probably in the infectious pathway that leads to preterm birth such that an early intervention is at least feasible. As another example, fetal fibronectin testing is at its best for predicting preterm birth when it is assessed beginning at 22 to 24 weeks of gestation. Whether this is sufficiently early in the process that leads to preterm birth to initiate an effective intervention is unknown.

The time of day of the sample collection may also be an important consideration for the evaluation of various markers. In most studies of preterm birth, little attention is paid to the aspect of specimen collection timing. For example, salivary estriol levels demonstrate diurnal variation; the highest levels are noted at night, and the lower levels are noted throughout the daytime. In addition, the timing of specimen collection in relationship to other interventions may need to be considered. Corticosteroid administration may suppress salivary estriol levels for up to 6 days after maternal treatment.

Whether the preterm birth that is predicted by a marker is an early or late preterm birth should also...
be considered. For example, salivary estriol predicts late preterm births quite well.\textsuperscript{25,28} However, the data that are available suggest that a high salivary estriol is not particularly good at the prediction of earlier preterm births. Because the amount of morbidity and death in 36-week preterm births is low and current medical practice makes little attempt to prevent these births, being able to predict preterm births at these later gestational ages is of little importance.\textsuperscript{25,28}

**Predictive values**

A full discussion of predictive values in tests that are used to predict preterm birth is not possible here. However, the predictive values of any preterm predictive test (including sensitivity and specificity) and positive predictive values generally should be high for the test to be useful. It is difficult to offer specific guidelines, because tests that are not very sensitive or specific may still be useful if the intervention that is applied ultimately to those patients with positive test results is highly effective, safe, and inexpensive. Less effective, less safe, and more expensive interventions should require very high predictive values for the proposed tests. One interesting use for a predictive test is based not on the above measures but instead on the negative predictive value. For example, some investigators have found a given test’s negative predictive value (ie, the ability to predict who will not have a preterm birth) to be useful and cost saving. Currently, fetal fibronectin is used clinically because of its high negative predictive value; thus, women with preterm contractions who have negative fetal fibronectin test results are extremely unlikely to go on to have a preterm delivery and may be sent home with some degree of confidence.\textsuperscript{29}

**Classification of types of biologic markers**

Because there are so many potential biologic fluid markers of preterm birth, some sort of framework is necessary to divide markers into categories. A useful way of categorizing these markers is to divide them into the following types of substances:

Placental proteins include \( \alpha \)-fetoprotein, major basic protein, and placental isoferritin. It is likely that these proteins leak either into amniotic fluid, into plasma, or into cervical and vaginal fluid as disruptions in the placenta or membranes occur. Therefore, when elevated, they may serve as predictors for subsequent preterm births, although they may have no actual role in the pathways that lead to preterm birth.

Placental protein hormones such as corticotropin-releasing hormone, adrenocorticotropin, prolactin, and human chorionic gonadotropin could predict preterm birth in various fluids either because of an increase in production or because of increased leakage from placental sites.

Non-protein hormones levels that are produced in a variety of tissues, which include estrogens, progestins, relaxin) may rise or fall in the time period preceding a preterm birth.

Non-hormonal proteins such as alkaline phosphatase or ferritin are produced in the placenta but also in a number of extrauterine sites. These proteins often appear to be produced in response to inflammation.

Micronutrients, which include zinc, iron, various vitamins (such as folic acid), and other markers of nutritional status, have been purported to show some relationship to spontaneous preterm delivery.\textsuperscript{30,31}

**Infection-related factors**

In the last decade, it has become increasingly clear that infection/inflammation has a strong association with preterm delivery and especially early preterm delivery.\textsuperscript{32-35} Various estimates suggest that approximately 80% of the preterm births that occur at \(<1000\) g or at \(<28\) to 30 weeks of gestational will be associated with either histologic chorioamnionitis or organisms in the placental membranes. Therefore, great effort has been spent to define markers of inflammation, which to date include substances as disparate as C-reactive protein; ferritin; the interleukins; a wide variety of chemokines, cytokines, and defensins; and various bacteria and bacterial products. Tables I and II, from a previously published paper,\textsuperscript{33} summarize the tests that have been shown to have positive results and are thought to be associated with increased risk of infection or inflammation-related preterm birth. Many of these substances can be produced by the mother, the fetus, or the placenta. Because these substances may migrate across compartments, their presence or elevation in any specific fluid does not mean that they originated in that fluid or compartment.

**Types of fluids**

Another way to categorize markers is by the fluid in which they are found.

**Cervical and vaginal fluid**

Over the years, investigators have evaluated a number of substances that have been found in cervical or vaginal fluids for their ability to predict spontaneous preterm birth. Many of these substances, but not all, involve various bacteria and viruses or their byproducts. For example, vaginal colonization with gonococcus, Chlamydia, group B streptococcus, herpes virus, and many other infective agents have been evaluated for their relationship to preterm birth.\textsuperscript{34} This immense literature can be
summarized in the following manner: Virtually every vaginal organism has been associated with preterm birth in at least 1 study. These relationships are generally inconsistent from study to study. Additionally, it appears that, the more one considers confounding factors, the less it appears that vaginal colonization with individual organisms is associated with a spontaneous preterm birth.

Bacterial vaginosis, which was diagnosed by Gram stain by the Nugent criteria or by the Amsel criteria, on the other hand, is associated consistently with approximately a 2-fold increased risk of spontaneous preterm birth. Nonpregnant women with bacterial vaginosis are more likely to have a chronic plasma cell endometritis with organisms that are associated typically with bacterial vaginosis. Therefore, in nonpregnant women, bacterial vaginosis is likely a marker for an upper genital tract infection. It is also clear during pregnancy that bacterial vaginosis is associated with (or a marker for) an increased risk for intrauterine infection before the rupture of membranes or before preterm labor. In addition to specific organisms, a number of other characteristics of vaginal fluid have been examined as predictors of spontaneous preterm birth. Many of these predictors are associated with bacterial vaginosis and include the presence of various organic acids, various bacterial or white blood cell enzymes, a high pH, the presence of polymorphonuclear leukocytes, and clue cells. Bacterial products (such as sialidase and mucinase) also have been used as markers for the subsequent onset of spontaneous preterm labor and PPROM.

Other substances in the cervicovaginal fluid that have been associated with spontaneous preterm birth include high values of various cytokines, such as interleukin-6 (IL-6). Other markers of inflammation that are produced by the pregnant woman herself are being evaluated as markers for preterm birth. These include substances such as monocyte chemotactic protein 1 and insulin-like growth factor binding protein 1, a count of white cells in vaginal fluid, white cell products (such as defensins and lactoferrin), and various matrix metalloproteinases. Recent work has also suggested that markers of collagen synthesis and degradation may be useful for the identification of women who are at risk of preterm birth.

To date, however, the best marker of spontaneous preterm birth is the presence of fetal fibronectin in the cervix or vagina. It appears that this particular protein, which is produced by fetal membranes and trophoblasts, normally forms a biologic glue that adheres the fetal membranes and placenta to the decidua. After approximately 20 weeks of gestation, fetal fibronectin (at values of >50 ng/mL) generally is not found in the cervix or vagina, probably because of the very tight application of the membranes to the decidua, which occurs at <20 weeks of gestation. In a series of studies, we and others have demonstrated that, when fetal fibronectin is present at >50 ng/mL in the cervix or vagina from approximately 22 to 24 weeks of gestation onward, it is a very powerful predictor of subsequent preterm birth. In 1 study, for example, at 24 weeks of gestation, the presence of fetal fibronectin in the cervix or vagina was associated with approximately a 60-fold increase in spontaneous preterm birth over the next 4 weeks, with a sensitivity of >60%. At present, there is no better marker for subsequent spontaneous early preterm birth than the presence of fetal fibronectin.
in the cervix or vagina at approximately 24 to 26 weeks of gestational.

**Amniotic fluid**

Substances in amniotic fluid also serve as excellent markers for spontaneous preterm birth. The fact that amniotic fluid generally is not obtained from asymptomatic women, except at the time of amniocentesis for genetic indications, makes these studies difficult to interpret. However, in the 16 to 18 gestational week range, it has been demonstrated that increased IL-6 levels and the presence of *Ureaplasma*, which is diagnosed either by culture or polymerase chain reaction, are associated with subsequent rupture of the membranes and preterm labor as late as 32 weeks of gestation.\(^5\) Wenstrom et al\(^5\) and Ghindini et al\(^5\) have demonstrated that, the higher the IL-6 level at the time of amniocentesis, the greater the likelihood of spontaneous fetal loss within the next 4 weeks. In another study, Wenstrom et al\(^57\) demonstrated that elevated IL-6 levels at 16 to 18 weeks of gestation were also associated with a subsequent preterm birth as late as 32 weeks of gestation. Other markers (such as various matrix metalloproteases, angiogenin, collagen synthesis/degradation markers, and other inflammatory proteins) have also been investigated in asymptomatic women.\(^58-61\)

In symptomatic women (ie, those women who enter the hospital with contractions and cervical change), it is clear that many amniotic fluid markers of infection (eg, various cytokines [IL-1, IL-6, tumor necrosis factor–α], white cells, defensins, various metalloprotei-
nases, and low glucose levels) tend to predict which women will be delivered early versus those women who will not.\(^62-64\) Whether one considers these to be true markers or not is debatable, but there is little doubt that, in symptomatic women, markers of inflammation in the amniotic fluid significantly differentiate women who will be delivered sooner versus those women who will not be delivered until later.

**Urine**

Another biologic fluid that can be used for the study of markers for the prediction of preterm birth is urine. In urine, the level of various hormones and the presence of various organisms have been proposed as useful markers to predict subsequent spontaneous preterm birth. In addition, urine has been used to measure exposure to various environmental toxins and drugs (such as tobacco and cocaine). Because none of these agents are potent predictors of preterm delivery in themselves, their usefulness as markers is reduced. However, urine DNA examination for organisms such as *Chlamydia* and gonorrhea is quite useful for the prediction of vaginal or cervical colonization with these organisms.\(^11\)

**Saliva**

Saliva is an ultrafiltrate of plasma, and among the bodily fluids, it is the easiest fluid to collect. For these reasons, it is potentially useful as a fluid in which to measure a wide variety of substances. As an example, measurement of salivary cotinine has been used for years to confirm tobacco use. Recently, various hormones in saliva, especially estriol, have been evaluated for their potential relationship to spontaneous preterm birth.\(^25,28,65\) Unconjugated steroid hormones enter saliva principally through diffusion. Thus, hormone concentrations are not very dependent on the rate of salivary production, and the concentration in saliva closely approximates the level of unbound hormone in plasma.\(^25\) As stated earlier, although women with a positive salivary estriol test result are at increased risk for preterm birth when compared with women with a negative test result, salivary estriol appears to be a better marker for late preterm births.\(^25,28,65\) Because these infants are at low risk for neonatal morbidity and death as the result of prematurity when compared with infants who are delivered at earlier gestational ages, the clinical usefulness of this biochemical marker is unclear.\(^25\) Limited data are available with respect to other salivary biologic markers in relation to preterm birth.

One limitation of the use of saliva for marker assessments is that levels of various substances can be confounded by a number of factors that include patient activity/posture and food consumption.\(^25\) Steroid hormones, such as estriol, also have large diurnal variations, and levels can be suppressed with concurrently administered corticosteroids.\(^25-27\) Disruption of the cuta-
neous barrier because of oral lesions, abrasions, or gingivitis may also allow maternal serum proteins to exude more readily into the saliva, thus falsely elevating the levels.

**Serum/plasma**

The final biologic fluid to examine for its ability to predict spontaneous preterm birth is plasma. Over the last several decades, hundreds of publications have attempted to evaluate various plasma (or serum) components for their ability to predict either spontaneous preterm labor or rupture of membranes. We have published data that show that high serum granulocyte colony-stimulating factor (G-CSF) and ferritin levels are among the strongest predictors of preterm birth; high α-fetoprotein, alkaline phosphatase, and high corticotropin-releasing hormone levels also seem likely to be useful for the prediction of preterm birth.\(^5,10,13,66,67\) Tables III and IV show a summary of the relationship between various markers, usually at the 90th percentile cutoff for the prediction of <32- and <35-week preterm birth from the National Institute of Child Health and Human Development Maternal Fetal
Medicine Network’s Preterm Prediction Study. We should note that for G-CSF, although the use of the 90th percentile was not effective, the use of the 75th percentile cutoff made serum G-CSF a highly predictive marker of preterm birth.

Multiple markers

In addition to evaluating individual markers for spontaneous preterm birth, our group has been interested in developing a multiple marker test for spontaneous preterm birth. As stated earlier, we found that the strongest biologic markers for preterm birth in maternal serum are α-fetoprotein, alkaline phosphatase, G-CSF, and cervicovaginal fetal fibronectin. Cervical length by transvaginal ultrasound scan, although not a biologic fluid marker, is also a powerful predictor. Most important, we found that overlap among the strongest biologic predictors for spontaneous preterm birth is small. This finding suggests that the use of a combination of serum tests (such as those named earlier) or the addition of some of their results to fetal fibronectin and cervical length testing may enhance our ability to predict spontaneous preterm birth. In fact, we recently have attempted to explore the potential for separate serum and cervical multiple marker tests to enhance the predictive value of the presently available serologic markers for spontaneous preterm birth. In fact, we recently have attempted to explore the potential for separate serum and cervical multiple marker tests to enhance the predictive value of the presently available serologic markers for spontaneous preterm birth. Therefore, because we believe that there are several pathways that lead to spontaneous preterm birth, this suggests that the use of several biologic markers together might be useful. Thus,

### Table III

<table>
<thead>
<tr>
<th>Factor</th>
<th>Source of fluid</th>
<th>Test cutoff</th>
<th>Percentage positive</th>
<th>Odds ratio: Cases vs control subjects</th>
<th>Significance (P &lt; .05)</th>
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<tbody>
<tr>
<td>Corticotrophin-releasing factor</td>
<td>Serum</td>
<td>90th*</td>
<td>10.6</td>
<td>4.3</td>
<td>2.7</td>
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<td>4.5</td>
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<td>1.3</td>
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<td>1.7</td>
</tr>
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<td>1.3</td>
</tr>
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<td>5.4</td>
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<td>10.9</td>
<td>1.0</td>
</tr>
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<td>Serum</td>
<td>90th*</td>
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<td>12.8</td>
<td>0.5</td>
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<td>Serum</td>
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<td>0.8</td>
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<td>6.1</td>
<td>3.9</td>
</tr>
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<td>Fetal fibronectin</td>
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<td>≥50 ng/mL</td>
<td>38.0</td>
<td>36.0</td>
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<td></td>
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<td>20.9</td>
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<td>24.0</td>
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</tr>
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<td>Short cervix</td>
<td>Ultrasound scan</td>
<td>&lt;25 mm</td>
<td>44.9</td>
<td>44.9</td>
<td>12.2</td>
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</table>


* Percentile.
the creation of a sensitive and specific multiple marker test for spontaneous preterm birth seems possible.

In the creation of a multiple marker test, issues such as patient convenience, ease of test performance, and costs are all important once acceptable levels of predictability are achieved. For this reason, in the National Institute of Child Health and Human Development Preterm Prediction Study, we chose not to evaluate fluids that were obtained by amniocentesis as tests for spontaneous preterm birth, even though elevated levels of bacterial products or cytokines in amniotic fluid have been shown to be excellent predictors of preterm birth.

On the other hand, it appears that a vaginal/cervical examination to obtain ultrasound data or to collect the fluids samples is acceptable to most pregnant women. Similarly, a blood test appears acceptable to most women. If the test is to be of widespread value, the handling of the sample must be relatively convenient. The more specialized handling that a specimen may require (such as immediate centrifuging and fast freezing for corticotropin releasing hormone), the less widely applicable the test is likely to be.

### Genomics/proteomics

Advances in molecular biology have lead to the emergence of 2 new marker approaches for the analysis of biologic systems and disease processes: genomics and proteomics. Genomics represents a study of genome-wide gene expression at the messenger RNA level to provide an integrated view of the relationship between the host genome, gene expression, and ultimate pheno-

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**Table IV  Biologic fluid tests for spontaneous preterm birth at <35 weeks of gestation that were obtained or available at 24 weeks of gestation in cases and control subjects**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Source of data or fluid</th>
<th>Test cutoff</th>
<th>Percentage positive</th>
<th>Odds ratio: Cases vs control subjects</th>
<th>Significance (P &lt; .05)</th>
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<td>Corticotrophin-releasing factor</td>
<td>Serum</td>
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<td>2.0</td>
<td>No</td>
</tr>
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<td>IL-6</td>
<td>Serum</td>
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</tr>
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<td>C-reactive protein</td>
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<td>9.6</td>
<td>1.0</td>
<td>No</td>
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<td>Fetal fibronectin</td>
<td>Cervix/vagina</td>
<td>≥50 ng/mL</td>
<td>22.8</td>
<td>9.1</td>
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<td>Gram stain score</td>
<td>Vagina</td>
<td>&gt; 9</td>
<td>22.8</td>
<td>1.7</td>
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<td>pH</td>
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<td>&gt; 5</td>
<td>38.1</td>
<td>2.3</td>
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<td>Chlamydia</td>
<td>Vagina</td>
<td>Positive</td>
<td>12.8</td>
<td>2.7</td>
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<td>Other predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous spontaneous preterm birth</td>
<td>History</td>
<td>Positive</td>
<td>43.3</td>
<td>4.3</td>
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<tr>
<td>Contractions</td>
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<td>Body mass index</td>
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<td>30.9</td>
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<td>Short cervix</td>
<td>Ultrasound scan</td>
<td>≤25 mm</td>
<td>36.8</td>
<td>5.5</td>
<td>Yes</td>
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* Percentile.
type or disease outcome. In contrast, proteomics is the study of the complete protein complement, or proteome, of the host in relation to the disease or phenotype of interest. Until now, research has focused on single protein markers or a combination of a relatively limited number of proteins that were measured in various body fluids. Genetic studies likewise have focused on gain (or loss) in function of single nucleotide polymorphisms in relation to spontaneous preterm birth. Several studies have shown a relationship between these polymorphisms and preterm birth and potential interaction with other markers, such as bacterial vaginosis. However, the results have been inconsistent. Lacking in these previous studies is the comprehensive evaluation possible with the newer genomic and proteomic technology. With research tools now readily available for both genomics (eg, gene array chips, gene sequencing) and proteomics (eg, protein array chips, mass spectrometry), the application of these techniques to the setting of preterm labor is underway. Although the use of these techniques is largely explorative in nature, detailed information regarding gene and protein expression patterns in women with preterm labor can be determined.

As with other markers, the use of such information is 2-fold: (1) to identify specific gene/protein patterns that have high sensitivity and specificity for preterm labor or PPROM, which is knowledge that may allow for potential targeted interventions to prevent preterm birth in high-risk women with specific patterns, and (2) to characterize and identify specific genes and proteins that are highly expressed in the setting of preterm labor and PPROM to gain further insights into disease pathophysiologic condition, which is knowledge that would potentially allow the development of novel pharmacologic tools to disrupt disease progression. Although the usefulness of these techniques has only begun to be explored in the setting of preterm labor and PPROM, the use of these new marker techniques to identify gene/protein patterns in women who are at risk for and/or with these pregnancy complications likely will lead to great advances in the years to come.

A recently published paper provides an example of the use of proteomics for preterm birth biomarker determination. In this study, the authors first inoculated bacteria into the amniotic fluid of rhesus monkeys and monitored the proteomic response over time. They identified several novel infection markers, including calgranulin B and a fragment of IGFBP-1. Later they identified the same proteins in the amniotic fluid of pregnant women with chorioamnionitis associated preterm labor. However, as stated earlier, because amnioncentesis is expensive and has some associated risks, amniotic fluid analysis is not an acceptable method of biomarker screening. The authors, therefore, took the next step and demonstrated that these proteins were measurable in maternal blood, and therefore may be useful as a biomarker for population risk screening for preterm birth. Further research will require determining appropriate diagnostic levels for a positive test and the predictive values for preterm birth for a positive test. They eventually will need to conceptualize a relevant intervention, and then test this intervention in those positive for these biomarkers in a randomized trial. Only, if the intervention successfully reduces preterm birth, will this biomarker, discovered through proteomic research, be appropriate to introduce into clinical practice.

**Clinical utility**

The identification of biomarkers that are associated with preterm labor and PPROM provides us not only with insights into the pathophysiologic condition of these pregnancy complications but also with tools that can be applied to identify women who are at the highest risk for these pregnancy complications to allow for targeted interventions. As previously discussed, any biomarker that is used to identify high-risk women for a given intervention should have high test sensitivity, specificity, and positive predictive value. To date, few markers have these characteristics. Another limitation to the use of specific biomarkers as a screening tool to identify women at high-risk for preterm birth is the fact that there currently are few interventions that have been shown to be of benefit to prevent or reduce the incidence of preterm birth. Clearly, a key attribute to any screening test is the availability of an effective intervention to prevent or reduce the disease that is being screened for. In the absence of such an intervention, the use of biomarker screening will likely be of continued limited clinical value.

Perhaps the following scenario is best example of this issue: Based on the strong association between elevated levels of cervical/vaginal fetal fibronectin and spontaneous preterm birth, this marker is a logical choice to target interventions to prevent subsequent spontaneous preterm birth in otherwise asymptomatic women. This is especially true because we demonstrated an association between increased fibronectin levels and chorioamnionitis. Antibiotics were thought to be potentially efficacious in these high-risk women to prevent preterm birth and thus was an exciting therapeutic intervention for evaluation. Indeed, a recent large multicenter randomized, double-blind, placebo controlled clinical trial that was conducted through the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network evaluated the use of antibiotic therapy for asymptomatic women who were found to be fetal fibronectin positive. Unfortunately, this targeted approach, which used the best available biomarker available, failed to prevent subsequent preterm birth.
The recently published studies on progesterone use to reduce preterm birth provide an interesting example of the use of a marker for preterm birth. In these studies, the risk marker that was used was a history of preterm birth, not a biologic fluid marker. Presumably with the reduction of preterm birth documented in these studies, this marker will be used to define the population that is appropriate for treatment. However, it is possible that various biologic fluid markers may have the potential to better define the populations in which this and other interventions will be even more effective. This raises the question of whether maternal serum progesterone concentrations are valuable as a marker for spontaneous preterm birth; however, mid-trimester levels of this marker are not associated with subsequent spontaneous preterm birth to date no study has used serum progesterone levels or other biomarkers to identify high-risk women for targeted progesterone therapy.

Comment

In conclusion, with all the studies of biologic fluid markers, it is important to understand whether the goal of the study is (1) to understand pathways that lead to preterm birth, (2) to define a high-risk population for future intervention studies, (3) to select a population in which a specific prevention intervention is to be used, or occasionally (4) to select a population that is at low risk so that they may be spared various interventions. Only once we have a clear understanding of how the study results are to be used, can we design studies that will produce the most useful information. For example, from a clinical perspective, research that is necessary to choose a usable biologic fluid marker for clinical care might first include the replication of the findings from the Preterm Prediction Study in a large, prospective study, by perhaps evaluating women at earlier weeks of gestation (<20 weeks). Next, women who test positive should be enrolled in clinical trials that test an intervention with biologic plausibility to reduce prematurity. Only when the use of a marker and subsequent treatment have been shown to result in a significant reduction in preterm birth should any single or multiple marker test for spontaneous preterm birth be introduced as part of routine prenatal care.

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Stress model for research into preterm delivery among black women

Carol J. Rowland Hogue, PhD, MPH,a,* J. Douglas Bremner, MDb

Department of Epidemiology, Rollins School of Public Health,a and Department of Psychiatry,b Emory University School of Medicine, Atlanta, Ga

KEY WORDS
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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 parturntion 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.

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...
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 postulated 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 poverty23,24 or dysfunctional family situations or a history of child abuse.26 These and other known risk factors do not account entirely for racial disparities in sexually transmitted diseases25,27,28 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 adrenocorticotropic 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. 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. 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. Stress age parallels McEwen’s 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. 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. 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.

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. Because of the relationship between chronologic age and decreasing dehydroepiandrosterone concentrations 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. An association between higher cord levels of dehydroepiandrosterone sulfate and higher birth weight and longer gestational age have been reported. 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. Possible candidate polymorphisms are the neurotransmitter-metabolizing enzyme monoamine oxidase A, which has been found to moderate the effect of child abuse among men, 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. There is also an age-dependent accumulation of mutations in human mitochondrial DNA. It is conceivable that individuals of the same
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. Alternatively, racism-associated stress may increase the overall impact of other stresses as well, through its impact on perception, coping responses, and psychologic and physiologic stress responses. 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. We have refined a model that was originally introduced in a discussion of black women’s health disparities 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. Jackson et al 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, Hogue 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. 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. 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 al 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. 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.

The significance of these genetic differences for preterm delivery is unknown. Although placental CRH production has been associated with the length of gestation, its expression appears to be regulated differently to CRH that is produced by the hypothalamus. 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.

### Racism as agent

The racism “agent” in this model operates in individual insults or discriminatory acts (what Jones 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. For their critical review of population-based studies of personally mediated racism, Williams et al 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. 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. In addition to the Perceptions of Racism Scale, the investigators included measures of daily hassles and self-esteem. 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 al.\textsuperscript{64} was completed, 2 additional studies have been published, with mixed results. Rosenberg et al.\textsuperscript{71} 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 al.\textsuperscript{72} 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 women\textsuperscript{73}), 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,\textsuperscript{74} a measure for blame reflection,\textsuperscript{73} an early life events scale,\textsuperscript{75} a depression inventory,\textsuperscript{76-78} and scales for anxiety and anger states\textsuperscript{79,80}), it will be necessary to determine their applicability to the particular population under investigation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 ongoing excess infant mortality rates among black infants.

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 ongoing 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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Racial inequalities in preterm delivery: Issues in the measurement of psychosocial constructs

Patricia O’Campo, PhD,a,b,* Ashley Schempf, BSa

Department of Population and Family Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md,a and Inner City Health Research Unit, St Michael’s Hospital, Toronto, Ontario, Canadab

KEY WORDS
Psychosocial construct
Measurement
Racial gap
Preterm delivery

Psychosocial risk factors for preterm delivery have been a topic of much recent research. By extension, the role of psychosocial risks in explaining the racial and ethnic gap in preterm birth is of increasing interest.7-11 Candidate psychosocial factors abound; examples of interest in the explanation of preterm birth and the racial gap in PTD are listed in the Figure.

The purpose of this paper is to provide an overview of important measurement issues involved when examining psychosocial factors of relevance to understanding the US racial gap in preterm delivery. The topic of the importance of each of the psychosocial factors for increasing the risk for preterm delivery or their role in contributing to the racial gap in preterm birth are discussed extensively elsewhere1,4-7,10-18 and is beyond the scope of this paper. Rather we focus here on a general set of measurement related principles that should be considered and addressed to improve investigation of the contribution of psychosocial factors to the racial gap in preterm birth. In an effort to present a comprehensive array of salient measurement issues, single topics are not discussed extensively and readers are encouraged to consult included references for additional information. We highlight those methodological issues and improvements that can be implemented with relative ease and use specific examples only to illustrate the principles and not to endorse any particular hypothesis.

Choose the psychosocial measure last

Although it may seem counterintuitive, the choice of the exact psychosocial measure of interest is one of the last considerations to undertake in the design of a study. One of the first considerations will be to identify the exact hypothesis to be examined and more specifically to
identify the pathway by which the proposed psychosocial exposure of interest is related to the outcome. The issue of intimate partner violence (IPV) as a potential exposure of interest provides a good example. The prevalence of IPV against women, which is an underrecognized exposure around the time of pregnancy, varies by race and social class. Moreover, the possible pathway from IPV exposure to preterm birth, and in particular, to the racial gap in preterm birth can also vary widely (Table I).

Without first knowing which pathway is of particular interest to the study, the exact measure of IPV cannot and should not be specified. Moreover, for topics such as IPV, it remains unclear whether IPV contributes to the racial gap in preterm birth, perhaps because relatively little is known about its role in promoting preterm birth; and it is likely that more than one pathway will be of interest to further our knowledge about the most and least promising mechanisms that can explain the observed associations. Clearly, a generic measure of IPV during or around the time of pregnancy will not allow for the investigation of the specific pathways that are identified in Table I. Rather, an IPV measure that captures information separately on physical abuse, domination, and forced sex is the only way that the various pathways can be investigated. Some examples of commonly used measures and the specific domains that are included are presented in Table II.

If we examine some of the most commonly used measures of IPV (such as the Conflict Tactics Scale), we can see that this measure is inadequate for our purposes if we are interested in more than one pathway by which IPV can lead to PTD or contribute to the racial gap in preterm birth. Although the revised Conflict Tactics Scale is an improvement, there are no measures of power, control, or domination within a relationship. Only the Measurement of Wife Abuse, which is rarely if ever used in studies of pregnancy outcome, includes questions about stalking. An additional concern is the appropriateness of many commonly used IPV measures for minority women given that most measurement tools have been developed on rather narrow populations and much of IPV research has excluded a focus on communities of color. Thus, rather than having the most commonly used set of questions drive the choice of measure to be included, carefully matching the questions to the specific hypotheses to be tested and knowing whether measures are appropriate for the specific populations under study are critical to ensure a greater understanding of the racial inequalities in preterm birth.

**Table I** Intimate partner violence and preterm birth: Multiple pathways from exposure to outcome

- IPV (physical abuse) may result in physical injury, which may lead to preterm birth
- IPV (domination of male partner over pregnant woman) may be a stressor leading to stress-related preterm birth
- IPV (sexual abuse) may lead to unintended/unwanted pregnancy, which may increase the risk of preterm birth
- IPV (stalking) may produce stress along with social isolation, leading to preterm birth via the combination of stress and a lack of buffering social support
- Multiple pathways as noted above can be operating together to increase the risk of preterm birth
Improve the measurement of socioeconomic position

One of the most important, yet relatively easy, methodologic improvements that can be researched concerning psychosocial factors and racial gaps in PTD is to improve the measurement of socioeconomic position. Epidemiologists and other public health researchers, in general, fail to account adequately for the role of socioeconomic position in racial inequalities research. Specifically, the use of single indicators of socioeconomic position (such as, education or categories of income) does not account fully for economic differences among the groups. There are several problems inherent in the use of single indicators or crude measures to control or adjust for the impact of socioeconomic position that make it less than ideal approach in the study of racial inequalities in health. The concept of socioeconomic position is complex, and one-dimensional measures (eg, education) do not fully capture the construct. In addition, the experiences that are associated with standard socioeconomic position indicators (income, education, and occupation) are not the same among different racial groups. For example, white families have approximately twice the income, 4 times the net financial assets, and a staggering 9 times the net worth of black families.

Wealth information is probably the most critical piece of data to collect if one is attempting to account for economic differences among race and ethnic groups. Wealth captures information, at a single point in time, on the household financial assets (eg, housing ownership, ownership of rental properties and businesses, investment income, vehicles). Net financial assets account for the household debt on these assets. Duncan and Peterson outline recommendations for short and long data collection instruments for wealth. In addition to wealth data, or if wealth information cannot be collected, then it is critical to collect information on income. They discuss important aspects of ensuring high-quality complete data on wealth and income that should be considered for those researchers who collect this information on surveys.

Adjustment with the use of a single or crude indicator of socioeconomic position results in problems of residual confounding for economic position when comparing health status or health care use among race or ethnic groups. The use of multiple indicators will minimize the degree to which residual confounding is a problem.

Avoid misclassification of exposure

Imprecise measurement of psychosocial constructs or poorly specified models diminish the ability to detect the effects of exposures. For example, single measures of stress or assessment of exposure to only one type of stressor may underestimate exposure. In addition, exclusive reliance on “objective” stress indicators (eg, number of life events or biochemical markers) without assessment of subjective appraisal and moderating resources would be inadequate. Several studies have now shown that only life events perceived as negative and stressful are associated with preterm delivery. Moreover, if measures of stress are detrimental only for vulnerable women or under certain conditions, then models that do not account for such interactions will incorrectly estimate the association between stress and PTD. Inadequate measurement or models that undermine the capacity to detect potentially true effects might also limit explanations of racial disparities in PTD.

Another source of misclassification might be introduced by measurement of exposure at cross-sectional time points, as average levels throughout pregnancy or as having occurred at anytime during pregnancy, if there are in fact critical periods of vulnerability to the effects of psychosocial factors. Little effort has been made to evaluate the presence of gestational periods of vulnerability to psychological factors, despite established knowledge of the existence of critical periods for exposures such as smoking and alcohol consumption. Most psychosocial research uses broad exposure categories such as “the experience of violence at any time during pregnancy” or “the average level of social support throughout pregnancy” rather than breaking these exposures down by month, trimester, or some other narrow time periods. The investigation of the existence of critical periods is likely to provide valuable insight into underlying mechanisms and may uncover effects that help to explain persistent racial disparities.

The likelihood of this type of nondifferential misclassification depends on the variability of exposure to

<table>
<thead>
<tr>
<th>Table II</th>
<th>Common measures of IPV: Domains measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement tool</td>
<td>Physical</td>
</tr>
<tr>
<td>Abuse Assessment Screen (AAS)</td>
<td>X</td>
</tr>
<tr>
<td>Conflict Tactics Scale (original)</td>
<td></td>
</tr>
<tr>
<td>Revised Conflict Tactics Scales</td>
<td></td>
</tr>
<tr>
<td>Measurement of Wife Abuse</td>
<td></td>
</tr>
<tr>
<td>Psychological Maltreatment of Women Inventory</td>
<td></td>
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</tbody>
</table>

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psychosocial factors throughout pregnancy and the length of the critical period. If women are exposed only within the critical period (highly unlikely) or if exposure remains relatively constant throughout pregnancy, the risk of misclassification is minimal. For example, levels of social support may be relatively constant within a period of 9 months, which would not produce misclassification in the event of critical periods. However, the occurrence of life events may be highly variable over a 9-month period, and there may be many women who experience life events, but not within the critical period for such exposure, who would be misclassified. The equivocal findings from studies of life events may be explained partially by this misclassification and by the absence of subjective appraisal. Thus, exposures that are highly variable should be measured with greater specificity.

To illustrate the impact of misclassification, we present a hypothetic example in which stress only late in pregnancy is associated with PTD, a finding supported by Hedegaard et al who observed a significant effect of stress, both life events and perceived stress, on PTD at 30 weeks of gestation but not at 16 weeks of gestation (Table III). At 30 weeks of gestation, the odds of PTD for a woman who experiences stress are twice the odds of a woman who does not experience stress. At 16 weeks, an irrelevant time period, there is no association between stress and PTD (odds ratio, 1.0). If exposure at anytime during pregnancy were used, the magnitude of the relation between stress and PTD is significantly reduced (odds ratio, 1.3) and would not have achieved statistical significance.

This example clearly illustrates the inadequacy of the use of “anytime during pregnancy” or cross-sectional exposure assessment when there is a critical period of impact. Moreover, anytime exposure assessment would be insufficient if the pattern of exposure were important, e.g. the chronicity or changes in exposure over time. Only a handful of studies that examined PTD or gestational length have measured psychosocial factors at multiple time points, and none of the studies measured it at >2 points during gestation. Yet these studies have shown differential effects and other studies report that changes in life stress are related to adverse pregnancy outcomes. Two additional studies have reported that the timing of acute traumatic events earlier rather than later in gestation is related to reduced gestational length.

Although it may seem a daunting task to collect data at multiple time points, especially monthly, Picciotto et al found that >85% of a population-based sample of women who delivered live births were able to report retrospectively the specific months in which they had been exposed to such things as common medicines, illnesses, lifestyle behaviors, and home chemicals. Considerable intratrusater variability also was observed, which suggests that women tend not to think of their exposures by trimester and that greater precision can be gleaned from monthly data. The potential variability of psychosocial factors, particularly the experience of violence and life events, supports the need to collect information on exposure over several shorter periods around the time of pregnancy and perhaps even prior to pregnancy in a life course perspective with effects from earlier exposure.

Although there are vast methodologic challenges facing those researchers who implement instruments of detailed data collection, such as the determination of the reliability of retrospective recall, addressing and overcoming these challenges would help to determine the true nature of an effect (i.e., critical periods, cumulative, relative change, or anytime exposure) and to guide future data collection. Moreover, we must begin to collect more precise data regarding the timing and patterning of psychosocial factors in diverse populations to assess its relevance and contribution to racial disparities. The potential underestimation of the impact of psychosocial factors by inadequate measurement necessarily limits their capacity to explain racial differences in PTD.

**Measure potential moderators**

Although we must do a better job of identifying the specific psychosocial factors that may occur disproportionately among black women, another avenue is to explore the role of moderators. The challenge in pursuing this route are (1) there are no universal moderators because they are specific to the exposures and outcomes of interest, and (2) to choose appropriate

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**Table III** Hypothetical example of women who are exposed to stress at different gestational ages

<table>
<thead>
<tr>
<th>Exposure</th>
<th>PTD (n)</th>
<th>Term (n)</th>
<th>Totals (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 30 weeks of gestation*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>20</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Not exposed</td>
<td>100</td>
<td>800</td>
<td>900</td>
</tr>
<tr>
<td>Totals</td>
<td>120</td>
<td>880</td>
<td>1000</td>
</tr>
<tr>
<td>At 16 weeks of gestation†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>12</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>Not exposed</td>
<td>108</td>
<td>792</td>
<td>900</td>
</tr>
<tr>
<td>Totals</td>
<td>120</td>
<td>880</td>
<td>1000</td>
</tr>
<tr>
<td>At either time during gestation‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>22</td>
<td>128</td>
<td>150</td>
</tr>
<tr>
<td>Not exposed</td>
<td>98</td>
<td>752</td>
<td>850</td>
</tr>
<tr>
<td>Totals</td>
<td>120</td>
<td>880</td>
<td>1000</td>
</tr>
</tbody>
</table>

* Odds ratio, 2.0.
† Odds ratio, 1.0.
‡ For this example, we assumed that one half of the women who were exposed at 30 weeks of gestation were also exposed at 16 weeks of gestation, regardless of the outcome, and that 10% of women were exposed at each time point.
moderators for a study, solid information about the pathway between exposure and outcome is desirable but often lacking in the literature. Therefore, although this approach is promising, progress in revealing moderators may be slow. In a conceptual framework of stress and PTD, Hogue et al provide a useful conceptualization of moderators as host and environmental characteristics that can alter the impact of an agent, in their case stress. Examples of host factors that may alter susceptibility to stress, violence, or discrimination include personal psychologic resources, coping style, and material resources. Locus of control or mastery has been shown to be related to either birth weight or gestational length in several studies. For example, Rini et al reported that the personal resources of mastery, self-esteem, and optimism influenced the length of gestation indirectly by reducing anxiety. Coping style (problem-focused vs emotion-focused) may also modify the effect of exposures. In addition, socioeconomic position confers differential access to material resources that may limit the impact of adverse psychosocial exposures. External environmental moderators might include social support and neighborhood characteristics (such as poverty, unemployment, and the activity of community groups).

In addition to the potential for racial differences in the prevalence of psychosocial factors and their moderators, these factors may have different effects among black versus white women. Failure to explore the potential for differences in the effects of psychosocial and other factors by race may hinder our ability to understand and explain racial disparities in PTD. A recent study of the influence of neighborhood characteristics on birth weight suggested that higher levels of neighborhood support improved birth weight among black mothers only and neighborhood economic disadvantage significantly decreased birth weight among black mothers only. Accounting for racial differences in these and other individual level effects helped to explain 60% of the racial differences in mean birth weight. Other studies have similarly reported that the effects of neighborhood socioeconomic characteristics on birth outcomes are stronger for black than white women. There is also some evidence that job strain may be more detrimental for birth outcomes among black women as a potential consequence of gendered racism.

Our current, albeit limited, knowledge of race-related moderators should underscore the need to consider and incorporate these and other potential interactions in analyses to further our understanding of the racial gap in PTD. Given our present knowledge of influential moderators, we should strive to consistently measure and incorporate them in analyses to arrive at more complete models and accurate effect estimates. Increasingly, multilevel analyses are also showing that other risks of individual characteristics besides race can be moderated by broader community level liabilities and assets. For example, Ahern et al found that, among black women with public insurance, the odds of PTD were highest in neighborhoods with low unemployment. However, better theory regarding the mechanisms by which neighborhood conditions influence health is needed to guide and inform multilevel analyses.

Careful evaluation of pathways

Greater emphasis should be placed on the explicit specification and testing of proposed pathways. For example, if emotional social support is being proposed as a buffer for stress, stress also should be measured. Likewise, the effect of instrumental support, which involves material and task assistance for such things as transportation, household work, food, and money, may depend on the need for such assistance. In which case need should also be measured to test the pathway. More recent research has supported a main effect of social support, independent of stress level, for which pathways have not been discussed adequately. In addition, the relation between social support and stress will depend on the measures that are chosen. Social support can be expected only to buffer stress when objective measures of stressors such as life events are used because the subjective perception of stress involves an appraisal of the magnitude of the stressor in relation to available coping resources. Thus, perceived stress actually may mediate the effect of social support or personal resources on pregnancy outcome.

Although 3 distinct pathways have been suggested to mediate the relation between stress and PTD by way of negative health behaviors, stress hormones that may initiate labor, and depressed immune functioning that leads to increased susceptibility to infection, there has been surprisingly little effort to comparatively evaluate these proposed pathways. Moreover, it is important to consider these potential mechanisms when building analytic models. Controlling for sexually transmitted infections and health behaviors would detract from the total effect of stress if such variables at all mediate its effect.

Frequently, studies attempt to investigate a potential pathway without linking it to the outcome or examine the relation between a psychosocial factors and PTD without testing a pathway. For example, Culhane et al found that perceived stress increased the risk of bacterial vaginosis in pregnancy but did not examine this potential pathway in relation to the outcome of PTD, although a subsequent analysis reported that stress partially accounts for the higher prevalence of bacterial vaginosis among black women. Likewise, Zambrana et al found that stress, among other factors, accounted
for differences in birth weight between black and Hispanic women but did not evaluate the potential pathways and mechanisms. Several other recent studies of psychosocial stress and PTD have not examined potential pathways.58-61

More research should attempt to link psychologic parameters and biomarkers in relation to pregnancy outcomes instead of relying on one or the other alone. Researchers also should be cognizant that levels of physiologic or psychosocial parameters may hold different meaning by race (potential for interaction). For example, corticotropin-releasing hormone levels have been reported to be lower among black women than white women at multiple gestational time points.1

Statistical techniques such as structural equation modeling and path analysis also can facilitate the simultaneous estimation of multiple pathways by accounting for correlated errors among related variables. For example, using structural equation modeling and path analysis, Feldman et al62 found that social support predicted birth weight independent of gestational age and that education and marital status influenced birth weight indirectly through a positive relationship with social support. This article reviewed the need for a future analysis of the mediators of socioeconomic disparities in PTD, Kramer et al63 also plan to incorporate structural modeling to assess the relative strength of various pathways from psychosocial factors to PTD. However, it is important to remember that, although this type of modeling is useful for the identification of a best fitting model of pathways, it is theory driven and relies on the researcher’s specification of appropriately conceptualized models.

**Promising new research**

The earlier discussion focused on the need for substantial methodologic improvements to our current approaches in studying the role of psychosocial risks as contributors to the gap in US black and white preterm birth rates. Because we attempted to focus on issues that can be remedied with relative ease, we did not touch on some of the more pressing needs of this area, such as the inclusion of measures of racial discrimination.58,60,64-69 Racial discrimination research is just gaining momentum and has focused almost exclusively on measures of interpersonal racism and not on institutional racism. The methodologic issues that face this particular psychosocial construct are numerous, and more research should be undertaken to remedy current limitations.

On the positive side, the state of current research on psychosocial risks and preterm birth is on the verge of exciting advancements. We are now just beginning to link psychosocial factors with biomarkers and physiologic mediators in such a way that can elucidate mechanisms and possibly suggest effective modes of intervention. Several large-scale national initiatives, which include the March of Dimes Perinatal Epidemiologic Research Initiative (PERI) and the National Institutes of Child Health and Human Development Community Child Health Research (RFA HD-02-008), have funded projects that do or will measure a variety of psychosocial factors, a host of associated moderators, and behavioral, immunologic, and endocrine pathways. The projects have the potential to address some of the issues that have been raised in this review to further our understanding of the contributors to racial disparities in PTD.

### References


Research strategies for optimizing pregnancy outcomes in minority populations

Thelma E. Patrick, PhD, RN,a,* Yvonne Bryan, PhD, RNb

University of Pittsburgh School of Nursing, Magee Womens Research Institute, and Director of Patient Care Services Research, Magee Womens Hospital, Pittsburgh, Pa,a and National Institute of Nursing Research, Office of Extramural Programs, National Institutes of Health, Bethesda, Md.b

KEY WORDS
Health disparity
Reproductive health
Pregnancy outcome

The elimination of disparities in pregnancy outcomes is a common goal of clinicians and scientists and requires the collaboration of many disciplines to address the complexities of this still-increasing perinatal health concern. This commentary synthesizes the presentations and dialogue from a multidisciplinary workgroup meeting that was sponsored by the National Institute of Nursing Research in 2003. Concepts that are central to our understanding of the development and expression of such disparities are summarized, and approaches that are recognized as important in multiple disciplines that include basic, clinical, and social sciences are presented. Research strategies to foster a multidisciplinary research agenda are presented as a basis for future endeavors to improve pregnancy outcomes.

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It is well known that much of the health disparity of preterm delivery (PTD), low birth weight (LBW), and other adverse pregnancy outcomes is associated with racial and ethnic groups who live under the burden of suboptimal social, economic, and health conditions. Despite efforts to improve pregnancy outcomes, the gap in maternal and infant mortality and morbidity rates is widening, with black women more likely to experience adverse outcomes. (See Gennaro in this supplement for a review of known disparities and research efforts to address disparities associated with pregnancy outcomes.)

Since the 1970s, expert panels from academic and governmental agencies have organized meetings to discuss the state of the science that undergirds perinatal care and outcomes.1 These work and consensus groups have strategically moved our understanding of this long-standing health concern from one of recognizing that differences do exist to identifying pertinent concepts and establishing research agendas. Although scientists from many disciplines participated in past meetings, the goal of increasing collaborative multidisciplinary biobehavioral research remains a major priority. The complexities of adverse pregnancy outcomes in minority populations likely will not be answered by a single approach but instead will require the consideration of multiple contributing factors to succeed in closing the gap.

The articles in this supplement are representative of those that were presented at this meeting, and the goal of this article is to synthesize these documents and to provide a synopsis of key gaps in our knowledge and future directions for research. We present major conceptual areas that merit multidisciplinary and collaborative focus from scientists who study adverse pregnancy outcomes. These areas are race.genetics, stress,
environment, health care delivery, interactions, and biobehavioral pathways.

Race/genetics

Race provides a means of classification that initially seems quite clear, and yet, race differs critically from other classification methods when potential interpretations of the underlying processes are considered. Some individuals view racial differences in disease as owing to genes; other individuals see race differences as the consequence of the lived experience of being of a particular race. It is important to note, however, that what we call race is not necessarily genetically homogeneous. In fact, there is as much difference in genetic patterns within race as there is among races.

Race is difficult to define and is a poor marker for genetic variation; however, race could serve as a proxy for other measures. Women who are foreign-born, regardless of origin, are less likely to have LBW infants than are native-born women, and several authors have reported negative outcomes that are associated with prolonged exposure to lifestyles in the United States among minority populations. Other research shows that one may exchange morbidities in coming to the United States. For example, Pima Indians who remain in their location of origin in Mexico do not show evidence of this same high incidence. Presumably, these 2 groups have come from the same region and the same genetic background.

Such disparities in outcome, which are attributed to the experience of living in the United States, prompt the question of racism. Racism combines beliefs about physical appearance (color) with the power to enforce those beliefs through a system of legal, economic, political, psychologic, and social controls that work to the detriment of people of color. These controls may be completely invisible to those individuals without color, yet ubiquitous to those individuals of color. For a person of color, history and experience inform this experience through a different filter, which is a filter that remembers prejudice, overt racism, and hatred.

Racism may play a role and can be evidenced at the individual, interpersonal, or institutional level. Racially based discrimination that is directed at a person or group can be experienced as chronic stress and, when internalized, can affect the individual through altered stress reactivity. Although spirituality and resilience are characteristics that may buffer some of the effects of racism, the resistance to stress these buffers provide is understood poorly. As for institutionalized racism, the perspective of sociocultural experiences and social stressors for black women are likely related to a long history and personal experience of prolonged structural barriers and discrimination that put them at disadvantage relative to accessing care and receiving the kind of care that they need. These barriers are based on dominant views, values, and norms, but understanding what constitutes a barrier and how it should be eliminated will necessitate the perspective of those people who are affected by it. Studies typically have examined race differences in residential environments as measured by community income and access to health care and consistently have shown that urban poverty, above and beyond its effect on maternal education and prenatal care, is detrimental to pregnancy outcome.

Stress

Stress is a ubiquitous experience, although the term stress has different meaning depending on the framework of the person who offers the definition. From a biologic perspective the term stress is used to describe any physical challenge that threatens or is perceived to have the potential to threaten the stability of the internal milieu of the organism (homeostasis). Stress is recognized universally as a contributor to disease and impaired functioning and has been studied extensively in relation to adverse pregnancy outcomes. In general, the physiologic adaptations of pregnancy preserve the integrity of the mother, placenta, and fetus; however, disruption of reproductive function in mammals is a well-known consequence of stress.

Research on stress is multifaceted and undertaken at many levels of analysis. Discipline differences in definition and measurement of stress have contributed to divergent findings. Although there is general agreement that stress plays a role in aging, there is less consensus about the precise nature of the relationship and the mechanisms that are involved. Predictions about positive and negative relations between stress and aging depend on the nature, time of exposure, intensity, and chronicity of stress. Health-related stressors become chronic strains in daily life for most older adults. Changes in profiles of psychologic functioning (cognition, self-regulation, well-being) suggest a distress syndrome that is indicative of a gradual breakdown of the psychologic system. This breakdown is linked to decreased well-being and death.

Life stress may compound the normal stressors that accompany pregnancy. Pregnancy may result in lost jobs, physical discomfort, difficulty performing physical work, and increased economic needs. Economically challenged women could be affected particularly by additional stressors because of their already diminished economic resources, which may result in further negative consequences. Findings from studies of such stresses in pregnancy require the precise review of the type and timing of stresses, the nature of the outcome, and attention to the life circumstances (race, socioeconomic
status, social support, and others). For example, Mackey et al.\(^7\) reported that black women with preterm labor (PTL) had higher fatigue, work stress, and future security concerns than black women without PTL. In contrast, white women who did not experience PTL were more likely to experience these same factors as compared with white women with PTL. These chronic stressors have a different effect than has been reported for acute psychosocial stress that occurs during the pregnancy. Psychologic distress in the 30th week of gestation, that was not present in the 16th week of gestation, was related to preterm birth, although such distress at 24 to 28 weeks of gestation was not related.\(^7\) In contrast, Hoffman and Hatch\(^8\) concluded an absence of evidence that acute life stressors that are experienced during pregnancy adversely affect fetal growth (LBW) or duration of gestation (preterm birth). Hogue and Hargraves\(^3\) suggested specific circumstances that impose stress on the experience of pregnancy, which included unwanted conceptions, poorer nutrition, less sufficient prenatal care, and stress that was associated with behavioral risks, but caution that these factors may function independently of socioeconomic status, because middle-class black women also are delivered of more preterm babies compared with their white counterparts.

Conceptualizations of stress that are reflective of the process and cumulative effects of living in stressful conditions are important when health disparities are examined. Three perspectives with particular relevance to the examination of racial differences in pregnancy outcomes are stress age, weathering, and allostatic load, because each of these perspectives account for the effects of stressful experiences on a person’s wellbeing.

Increasing maternal age has long been recognized as an indicator of high perinatal risk. Stress age is a term that connotes premature aging as a result of cumulative stress or a major traumatic event and thus imparts a similar risk as chronologic age. This cumulative stress may be continual over-exposure to life’s difficulties because of poverty or a particularly large number of stressful life events. It is suggested that DHEAS, which decreases as age increases, is a potential marker for this early aging. A second perspective suggests that age does not hold the same meaning for all people and that there exists an interaction between age and race/ethnicity such that certain groups age more rapidly than others, which includes experiencing a more rapid decline in reproductive health from repeated experiences with social, economic, or political exclusion. This more rapid aging, or weathering, occurs in response to a lifetime of the socioeconomic disadvantage and race/ethnic discrimination that are faced by many minority groups.\(^9,10\) (In this supplement, Rich-Edwards and Grizzard synthesize the literature on such cumulative stressors and their efforts on physiologic functioning.)

Allostatic load is the third conceptual view; however, this perspective links the experiences of stress with physiologic adaptation and markers that derive from the systems that are likely to be affected by stress. Chronic stress alters interpretations of stimuli and influences behavioral and hormonal responses to potentially stressful situations. These mediators are involved normally in adaptation but can also promote damage when they are dysregulated and over-active. The brain not only encodes information and controls the behavioral responses, but it is also changed structurally by those experiences. Structural changes in the hippocampus and amygdala, which are important brain structures for cognition and emotion, are representative of what may be occurring throughout the brain as a result of allostatic load that results from the chronic stress of a disorder such as depression. Such structural changes include dendritic debranching and hypertrophy, cell proliferation, and synaptic remodeling; they are produced by the combined over activity of stress hormones and endogenous neurotransmitters. These changes are very likely to be biased strongly by early life experiences.\(^11\) The findings from animal models thus provide a basis for the understanding of potential mechanisms of environmental and developmental determinants of individual differences in human stress reactivity and anxiety, depression, and a host of related systemic disorders.

The environment

The environment that we are exposed to by virtue of where we live (the air we breathe and the water we drink) and the environment of experience (the context of neighborhood) are of great interest. Thus, we define environment broadly to include such factors as the social milieu, socioeconomic forces, lifestyle patterns, discrimination, the context of neighborhood, and the specific environment exposures.

The neighborhood is residential environment and the major source of experience and interaction. The context of the neighborhood is one that can offer protective or harmful health exposures, although more is known about the negative effects of the social environment. A disproportionately large percentage of black women reside in impoverished urban ghettos, communities that are infiltrated with violence and illicit drug traffic.\(^4\) Such community-wide strain is detrimental to pregnancy outcome. It may be associated with negative health behaviors (such as cigarette smoking, alcohol intake, and illicit drug use). Unfavorable perception of the residential environment (that is, residing in a community that one rates as “bad”) is a chronic stressor, particularly for women who do not have the resources to live elsewhere. This low rating of the residential environment
Health care delivery systems/health behaviors

Racial inequality may function both as a psychosocial stressor that directly alters physiologic response and as a structural factor that limits access to quality health care. The style of health care delivery, access to care, and education are all factors that participants noted as impacting pregnancy outcomes. A shortage of minority health care providers may influence the nature of care provided and the perception of care received. Minority women report that they receive less prenatal education on topics such as sexually transmitted infection, family planning, and preterm prevention. They are also less likely to receive ultrasound examination, tocolysis, or amniocentesis. In the context of interventions to improve health care delivery in high-risk populations, there have been positive effects on pregnancy outcomes.
This neglect of personal health is evidenced in many ways throughout pregnancy. Adherence to prenatal vitamins, which may be seen as a general nutritional supplementation, may have specific effects that improve pregnancy outcome. For example, folic acid, which is a component of prenatal vitamins, is protective against cardiovascular and neural tube defects in infants, and there is evidence that antioxidant properties in vitamin C may provide a protective effect for the maternal vasculature.

The elimination of racial and ethnic disparities requires a greater understanding of the factors that contribute to disparities in resources and socioeconomic status, behavior; access to, distribution of, and availability of health care services; and quality of health care services. Even a factor as seemingly obvious as appropriate nutrition levels is difficult to quantify because isolating it from socioeconomic variables in problematic. Analysis is further confounded by the interrelationship of prepregnancy weight to weight gain during pregnancy.

### Biobehavioral pathways

Maternal psychosocial stress, which includes the stress of infection and racially based discrimination, can be linked to biologic mechanisms that are associated with PTD and LBW. Stress appears to decrease immunity, thereby leaving the host susceptible to infection. Stress-induced changes may be caused, at least in part, by physiologic mechanisms that involve the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. If the stress activation is chronic, it can then result in allostatic load or the inability to achieve stability in the face of stress. Elements of “weathering” (such as poverty, racism and family functioning) can lead to vulnerability before conception by alterations in hypothalamic-pituitary-adrenal reactivity and degradation of the immune response and to risk factors for PTD (such as elevations in corticotropin-releasing hormone, hypertension, preeclampsia, and inflammatory responses) that are associated with PTD/LBW.

Behavior and biologic condition should be linked in pathways that point to systemic and cellular functioning and likely molecular and genetic markers. As noted by Goldenburg, Goepfert, and Ramsey (in this supplement), the physiologic adaptations of pregnancy increase the complexity of such pursuits. Vascular and immune changes and different rates of secretion of steroid and peptide hormones are evident throughout pregnancy. These differences preclude a direct transfer of discoveries in other systems because we must first establish a means of assessing such markers in the context of pregnancy, establish usual response patterns and normal values, and then interpret what these markers mean.

### Implications for research

A multidisciplinary approach must be one of partnering, cooperating, and valuing. For a problem as complex as health disparity in pregnancy outcomes, there is an infinite array of potential research directions and unanswered questions. To focus our discussion, we provide a synopsis of those concerns that optimally will be addressed through multidisciplinary work.

The traditional investigative approach to the black: white disparity in infant birth weight has been to compare the effect of individual risk factors between the races. This approach is based on the premise that such factors differ in quantity between the races, but exert similar effects in black and white patients. This conceptual model does not address adequately the reality that black and white patients rarely reside in the same community. Most black women do not experience a PTD or LBW but live within the same culture and environment as those who do. These differing outcomes in a like environment constitute the appropriate comparison group for the study of etiologic risk factors for PTD and LBW.

Simultaneously, determination of the contribution of social environmental and cultural forces, of psychosocial constructs, and of behavioral and physiological responses to the risk of PTD will require more than commonly used mathematic models that produce statistical associations between variables that are obtained through traditional qualitative epidemiologic research. Research that crosses disciplinary boundaries must focus on more complex modeling, rather than the search for cause and effect, in the pursuit of understanding disparities in adverse pregnancy outcomes. There are many implications for variable definition and selection and study design that should be addressed in future research design. Those studies that focus at a single point in time and a single level of measurement will not address these concerns adequately.

Study design must also take into account the exposure, the process, and the outcome. There are adequate numbers of descriptive and association studies that document that stress has an effect on pregnancy outcome. The nature of the outcome is influenced by the nature, timing, and intensity of the stress exposure. By designing studies that are based in hypotheses of a pathway that is affected by the stressor to result in the adverse outcome, we can provide biochemical evidence of the presence or absence or markers and outcomes in the context of a specific stressor. From such specificity, we will be able to implement and test interventions that are appropriate to the circumstance and outcome, rather than provide additional description at the more global level. In addition to stress, exposure and outcome that would benefit from such an approach are investigations of the role of (1) environmental and
occupational factors (eg, exposure to chemicals in the home and work environment, indoor and outdoor air pollution, contaminants in the food supply); (2) nutrition, by the consideration of multiple aspects such as prolonged fasting (by choice or imposed by life circumstance), micronutrients, and the effects of culture on diet patterns and physical activity. Further, we must be cognizant that our failure to detect some socioeconomic or lifestyle stressor that influences outcome does not mean that the association does not exist. We may have a poverty in the means of measurement. (See O’Campo and Schempf in this supplement for a discussion of measurement concerns.)

Important insights can be missed when the focus of the research is limited to the exposure with the observed negative outcome in the absence of an assessment of potential mechanisms. Studies of specific stressors and adverse pregnancy outcomes should specify the pathway by which the exposure is associated to the outcome, and measure associated biomarkers, such as specific stress hormones or neurotransmitters, as is suggested by the “weathering” hypothesis, or metabolic outcomes, as is suggested by the concept of allostasis. Additionally, when stress is measured, it is necessary to differentiate between stressors, stress buffers, and stress responses. Stresses in the environment vary by ethnic background and acculturation issues. Potential buffers like hardiness, resilience, and social support systems may mitigate some effects of stress. To design effective interventions, the mutability of risk factors needs to be considered. Interventions such as increased social support and other means of increasing invulnerability of the host to the insult are important and may require collaboration with basic scientists to understand what is possible to change.

With respect to methods, studies focused on new or novel methods, conceptual models, data analytic approaches, or the development and testing of culturally sensitive disparities in PTD and LBW (such as lifestyle exposure, sociocultural factors, risk factors that are associated with “weathering,” data mining techniques) are sorely needed. Interventions that target specific physiologic pathways and biochemical markers are known to be associated with poor pregnancy outcomes and include serial measurements to ascertain critical time periods.

We must organize collaborations among basic, clinical, and social scientists to focus on delineating risk and protective factors and biologic pathways with the use of interdisciplinary theoretic and methodologic approaches to answer the following questions: What risk factors for poor pregnancy outcomes are mutable? How are biologic phenomena impacted? What are the biologic markers of risk? These studies should include the identification of biomarkers in the fetus, mother, cord, and placenta and gene/environment interactions and the assessment of specific animal models to study preterm birth and LBW.

In an effort to accelerate the identification of candidate markers or gene/environment interactions, descriptive work could focus on smaller groups to find qualities that might represent micro aspects (such as genes) that give some groups the ability to survive hazards differently. Differences in the geographic origin of individuals provide examples of this concern. In addition, the complexity of the adverse outcome must be understood. PTD is a heterogeneous disease that is seen phenotypically with varying times of onset and severity of the disease. Therefore, PTD is probably not the result of a single gene disorder but rather of gene/gene interactions or gene/environment interactions. Maternal candidate genes have been studied, but there should be comprehensive study of maternal, fetal, and placental genes to understand gene expression at the maternal-fetal interface during early human development.

Research should transcend the pregnancy for causative factors. It has yet to be determined whether these differential health trajectories among nonpregnant women accurately characterize women’s health during pregnancy or explain the differential maternal age patterns of poor birth outcomes. Further, if social inequality affects the health of young adult women differentially, then one would expect to see variation in maternal age trajectories of poor birth outcome among black women, with respect to social class. Adverse pregnancy outcomes must be viewed from the perspective of their lifelong relevance to health. There may also be an intergenerational effect of these experiences and associated risks factors and fetal exposures to these factors may trigger this risk in the next generation.

Studies also are need to focus on acute and chronic stress, with special attention to measures of stressors and stress responses that include the role of antecedent and concurrent environmental exposures as risk factors for pregnancy outcomes (eg, Are there familial patterns or patterns of acquired risk? Are all stressors associated with some biologic phenomena? How are additive and interactive effects linked with PTD and LBW?).

There is an increasing amount of translational research that is beginning to connect the basic research to clinical outcomes of individuals who are exposed to a variety of physical and social exposures. A major goal of studies on this important topic is to define the times in development and strategies for intervening to prevent or reverse the effects of adverse early life experiences. Although prevention is clearly the preferable route, some degree of reversal of psychopathologic and pathophysiologic factors that are caused by early life adversity appears to be an achievable goal.

Finally, there is a need for interventions to test the impact on pregnancy outcomes of culturally competent preconception and prenatal care and access to care and linkages with public health and social services. The testing of such interventions as the effectiveness of social
supports, home visitation, and other approaches that mediate adverse psychologic, social, and environmental effects are important but will require collaboration with basic scientists to understand how resistance or protection can be improved and how PTD and LBW can be prevented.

Comment

Disentangling the underlying psychosocial and biologic mechanisms that are responsible for racial and ethnic variations in LBW and PTD and the elimination of or significant reduction of this variation is an ongoing challenge to research in this area. The inability of research efforts to isolate a single cause for the persistence of the black-white gap suggests a problem that is multifactorial in genesis and will require a multidisciplinary approach. In our workgroup, there was consensus that a multidisciplinary approach allowed participants to learn from others’ perspectives and that research in one area (such as research on stress and stressors in the psychosocial context) can build on research in another area (eg, biologic responses to stress that can influence poor pregnancy outcomes). Stress is one of those areas about which much is known about psychologic concerns and physiologic pathways of acute and chronic stress and thus may be an ideal area for early multidisciplinary work.

The solution to the puzzle of disparate pregnancy outcomes requires all of the strategies that we discuss but perhaps most importantly an integration of studies of biologic mechanisms and susceptibility and epidemiologic and behavioral and health services approaches (summary panel group). This is a significant time for scientists and clinicians who strive to improve pregnancy outcomes, particularly as experienced in different racial or ethnic groups. We benefit from conceptualizations of biologic condition, behavior, and environment that provide distinct measures and insights regarding experiences, exposures, and outcomes. As this science advances, we have been able to characterize biochemical differences and behavioral associations in pregnancies that are affected by preterm birth and LBW. In addition, there is recognition of the importance of life experiences and process in relation to health status. These perspectives, however, serve as “snapshots” taken by scientists who are working in parallel rather than in partnership, and the cause of persisting racial-ethnic disparities remains largely unknown. Assessment of differential exposures to protective and risk factors during pregnancy (eg, current socioeconomic status, maternal risky behavior, prenatal care, psychosocial stress, and perinatal infection) tell us little about the life experiences and the consequences of such experiences.

Much of the disparity of PTD and LBW is associated with racial and ethnic groups that live under the burden of suboptimal social, economic, and health conditions. However, poverty, race, and ethnicity are not the only contributing factors and, in and of themselves, do not explain the disparities in pregnancy outcomes between white and non-white patients.

References