Preterm Birth: Causes, Consequences, and Prevention

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SECTION II

CAUSES OF PRETERM BIRTH

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Behavioral and Psychosocial Contributors to Preterm Birth

ABSTRACT

Although individual behaviors have not been proven to have a strong influence on the risk of preterm birth, consistent evidence suggests that a constellation of favorable lifestyle factors are associated with more favorable pregnancy outcomes. These include a reduced risk of preterm birth among women who engage in leisure time physical activity, women who do not use cocaine, and those who have a favorable diet. There is clear evidence that a favorable lifestyle and a greater degree of health consciousness are associated with a reduced risk of preterm birth above and beyond what can be measured effectively and controlled in observational studies. Despite the lack of success in pinpointing behaviors that affect the occurrence of preterm birth, continued efforts are needed to better understand and ultimately pinpoint the aspects of a favorable lifestyle that are associated with a reduced risk of preterm birth. The results of research on psychosocial factors and preterm birth have accumulated rapidly in recent years. What is most clear from this large body of evidence is that psychosocial factors should not be grouped together as if they were one risk factor. Rather, they must be studied as the distinct theoretical risk factors that they are. Evidence indicates that some psychosocial factors in the etiology of preterm birth include major life events, chronic and catastrophic stress, maternal anxiety, personal racism, and lack of support.

This chapter reviews a number of individual-level factors that have been thought to contribute to preterm birth (birth at less than 37 weeks of gestation), including the available evidence for each factor, with an emphasis on the data and findings from recent and more definitive studies. The section on behavioral factors covers tobacco use, alcohol use, illicit drug use, nutrition (prepregnancy weight, weight gain in pregnancy, dietary composition, and fish and fish oil consumption), sexual activity, physical activity, employment, and douching. The section on psychosocial factors includes findings on stress (life events and chronic and catastrophic stress), emotional responses and affective states (anxiety and depression), racism, social support, personal resources, and intendedness of pregnancy. Suggestions for the understanding and prevention of preterm delivery on the basis of the review of the effects of these individual-level factors appear at the end of the chapter.

BEHAVIORAL INFLUENCES ON PRETERM BIRTH

A special interest in behavioral influences on preterm birth is well justified, given that these are subject to change and could reduce the frequency of preterm birth directly. As previously reviewed in some detail (Berkowitz and Papiernik, 1993; Savitz and Pastore, 1999), a large number of observational studies of a range of health behaviors, including tobacco and alcohol use, nutrition, and physical activity, have been conducted. Although each of these behaviors poses specific challenges in discerning cause-and-effect relationships, two key, generic concerns crosscut them all. First, it is a challenge to measure many of these behaviors with accuracy because of their inherent complexity, the inability of individuals to completely recall past behaviors (e.g., diet and physical activity), or the stigma associated with the behavior (e.g., alcohol and illicit drug use). The challenge is especially heightened for women who are pregnant. This inaccurate recall ability is accompanied by the potential for a distorted recall of the facts when these behaviors are assessed after pregnancy outcomes have occurred, as well as by a likely dilution of measures of association because of random error. Second, the decisions about these behaviors that women make render them highly susceptible to confounding, in which any true causal effects of the behavior of interest on preterm birth are distorted by the association of that behavior with antecedent factors like socioeconomic conditions or with other behaviors. For example, smoking during pregnancy has become increasingly strongly linked to lower socioeconomic condition, much more so than smoking by other segments of the population (Cnattingius, 2004), so that isolation of the effect of smoking per se from the socioeconomic context is challenging. In addition, unfavorable health behaviors tend to cluster, so that

women with poor diets often also exhibit other potentially detrimental behaviors, such as a lack of physical activity, and vice versa.

For a number of these behaviors, observational studies are inherently limited, no matter how carefully conducted and how attentive investigators are to controlling for other exposures (which are themselves difficult to measure accurately and to thus fully control). Nonetheless, when considered in conjunction with other lines of research involving mechanistic studies and randomized trials, observational studies of behavioral influences on preterm birth, when it is feasible to conduct such studies, have been highly informative. The subsections that follow review tobacco use, alcohol use, illicit drug use, nutrition, employment, physical activity, sexual activity, and douching.

Tobacco Use

Cigarette smoking is recognized to be among the most prevalent, preventable causes of adverse pregnancy outcomes. Smoking is strongly related to placental abruption, reduced birth weight, and infant mortality (Cnattingius, 2004); but the relationship of cigarette smoking to preterm birth is rather modest and not entirely consistent. The influence of smoking on pregnancy outcome is dependent on whether it occurs in the later part of pregnancy, and no increased risk has been detected for former smokers who quit before the onset of pregnancy or early in pregnancy.

Many studies have examined the association between smoking and preterm birth, as reviewed previously (Berkowitz and Papiernik, 1993; Savitz and Pastore, 1999), and they generally find modest associations. Recent studies continue to show such a pattern (Cnattingius et al., 1999; Hellerstedt et al., 1997; Lang et al., 1996; Savitz et al., 2001; Wen et al., 1990; Wisborg et al., 1996). However, some reports suggest a stronger association (Nordentoft et al., 1996) and others suggest no association at all (Goldenberg et al., 1998). The variability in results is limited, and evidence of relative risks (RRs) of about 1.2 to 1.5 for smoking 10 to 20 cigarettes per day and an RR of 1.5 to 2.0 for smoking 20 or more cigarettes per day is fairly consistent throughout the literature.

Some studies have suggested more pronounced effects for subsets of preterm birth or for subgroups of women. For example, a few studies (Berkowitz et al., 1998; Harger et al., 1990) have found stronger effects of smoking on preterm birth presenting as premature rupture of membranes than on preterm births due to the spontaneous onset of labor or for medical indications. Given that a primary cause of medically indicated preterm birth is pregnancy-induced hypertension, which is less frequent among smokers (England et al., 2002; Newman MG et al., 2001), different patterns of smoking effects across preterm birth subtypes might be expected. Some studies

suggest greater or lesser effects of smoking among African American women than among white women in the United States (Lubs, 1973; McDonald et al., 1992), suggesting a race-smoking interaction, and among older mothers (Cnattingius et al., 1993; Savitz and Pastore, 1999; Wen et al., 1990).

Alcohol Use

High levels of alcohol use during pregnancy have obvious adverse effects on fetal development (AAP, 1993; Spohr et al., 1993). There is consistent support of an adverse effect for heavier users of alcohol; for example, women who have more than one drink per day, on average, have an increased risk of preterm birth (Albertsen et al., 2003; Kesmodel et al., 2000; Larroque, 1992; Lundsberg et al., 1997; Parazzini et al., 2003). Subject to the question of the accuracy of self-reported information on alcohol consumption and some variation across studies in the definition of "heavier alcohol use," recent data provide evidence of an association between moderate alcohol use and preterm birth (Savitz and Pastore, 1999). However, some studies reported modest inverse associations between the consumption of small amounts of alcohol and preterm birth, but this may be a result of a higher prevalence of small alcohol use among women who are more socioeconomically advantaged (Albertsen et al., 2004; Kesmodel et al., 2000). A report from the Preterm Prediction Study, a recent large project to evaluate predictors of preterm birth, suggested a substantial reduction in the risk of medically indicated preterm birth in association with alcohol use (Meis et al., 1998). Research on alcohol use is limited by the quality of the self-report and the absence of biological markers that are well suited to epidemiological studies. Given that challenge, plus evidence that different effects may be observed at different dose levels and the suggestion that the effect differs by subtype of preterm birth, the issue of whether a relationship exists between alcohol use and preterm birth remains unresolved.

Illicit Drug Use

Marijuana and cocaine are the drugs that have been most commonly studied for their potential effects on preterm births. There is little indication that marijuana use influences preterm birth (Shiono et al., 1995). Either the psychoactive agents or the combustion products derived from the act of smoking could be harmful, but given that cigarette smoking produces only modest effects, it is unlikely that marijuana smoking would cause a discernible increase in risk through the inhalation of combustion products alone.

Cocaine has been much more intensively studied, and there is a sizable literature demonstrating an association between cocaine use and preterm

birth (Holzman and Paneth, 1994). Cocaine users experience an approximately twofold increased risk of preterm birth compared with that for nonusers. Although plausible preterm birth-related mechanisms of action of cocaine involving vasoconstriction have been detected and the association is found with reasonable consistency, there are real uncertainties regarding whether the association is causal. First, women who use cocaine during pregnancy often have other strongly associated lifestyle factors that could well constitute the underlying cause of preterm birth, such as infection or poor nutrition. Second, the ways in which cocaine use is detected may make identified cocaine users a particular subset of all cocaine users. That is, when screening is done on the basis of a suspicion or a known history of drug abuse, the women who are found to be positive for cocaine use may well be at higher risk of preterm birth on the basis of the factors that marked them as potential cocaine users rather than on the basis of the use of cocaine per se. Some studies suggest that more systematic assessments by the use of sensitive methods for the detection of cocaine use results in a smaller association or, in some cases, the absence of any association at all (Kline et al., 1997; Savitz and Pastore, 1999; Savitz et al., 2002a). Although there are many good reasons to discourage the use of cocaine during pregnancy, it is not at all clear that this is a major contributor to the etiology of preterm birth.

Nutrition

Prepregnancy Weight

Prepregnancy weight is not a behavior per se but is somewhat associated with patterns of diet and nutrition and thus is covered here. Evidence suggests that a low prepregnancy weight is associated with an increased risk of preterm birth (Kramer et al., 1995; Savitz and Pastore, 1999; Siega-Riz et al., 1996), although in the aggregate, the data in the literature are not consistent (Berkowitz and Papiernik, 1993). In general, the studies that do report on the association between low prepregnancy weight and preterm birth find modest associations, with RRs on the order of 1.5. In the Preterm Prediction Study, a low prepregnancy body mass index (BMI) was strongly associated with an increased risk of preterm birth, with the RRs being greater than 2.5 (Goldenberg et al., 1998), and obese women were at a markedly decreased risk of spontaneous preterm birth (Hendler et al., 2005). A recent meta-analysis of this topic found that prepregnancy BMI had little or no relationship with the risk of preterm birth overall (Honest et al., 2005), counter to the conventional wisdom regarding this association.

Weight Gain During Pregnancy

A low level of weight gain during pregnancy is associated with an increased risk of preterm birth (Berkowitz and Papiernik, 1993; Carmichael and Abrams, 1997), particularly for women who are not overweight or obese (Savitz and Pastore, 1999), with RRs for low weight gain and preterm birth being on the order of 1.5 to 2.5. Studies that adjust for infant weight by subtracting it from the total weight gain of the mother sometimes find that this adjustment eliminates the association (Berkowitz and Papiernik, 1993; Kramer et al., 1995). What is less certain is the extent to which the association reflects a causal effect of the weight gain on the risk of preterm birth compared with the extent to which the low weight gain and preterm birth are manifestations of some shared etiology. Weight gain during pregnancy reflects in part the duration of gestation (longer pregnancies allow more weight gain), which must be considered by calculating week-specific weight gain. Furthermore, weight gain in pregnancy is due not only to increased caloric intake and fat deposition but also to fluid retention.

Dietary Composition

A series of studies dating to the 1970s indicate that calorie supplementation during pregnancy does not reduce the risk of preterm birth. The challenges to addressing the hypothesized protective effects of micronutrient intake are profound. First, diet reflects individual choice and lifestyle, making it difficult to isolate the impact of individual micronutrients from one another or from the overall dietary patterns. Second, socioeconomic and behavioral correlates of diet can introduce confounding. Finally, accurate measurement of diet is extremely challenging, and with the rapid changes that occur over the course of pregnancy, it is particularly difficult to assess the composition of the diet and its relation to preterm birth. Randomized studies in both developed and developing countries have noted an absence of benefit from dietary supplementation in preventing preterm birth (Berkowitz and Papiernik, 1993). Furthermore, protein supplementation specifically has not been found to reduce the risk of preterm birth and possibly increases the risk (Berkowitz and Papiernik, 1993; Rush et al., 1980), as does multivitamin supplementation (Villar et al., 1998).

Relatively limited research has addressed the possibility that specific micronutrients, with the exception of long-chain fatty acids (discussed below), affect the risk of preterm birth. Limited iron levels in the bodies of pregnant women, which manifest as anemia, have been examined in a number of studies, but it is unclear the extent to which the results reflect actual iron intake. Iron deficiency anemia, which has been found to be correlated

with an increased risk of preterm birth in a number of studies, is unlikely to be an actual cause of preterm birth after the timing of measurement of iron levels (Berkowitz and Papiernik, 1993; Klebanoff et al., 1989) and the extent to which iron deficiency simply reflects maternal blood volume expansion rather than the influence of iron intake are taken into account. Serum ferritin reflects a response to inflammation and infection, not necessarily an influence of iron intake, and it is thus difficult to interpret serum ferritin levels as a marker of diet. Despite the reasons to question whether anemia is part of a causal pathway that leads to preterm birth, there is some consistency in the evidence from randomized trials that iron supplementation may reduce the rates of preterm birth (Villar et al., 1998).

Folate has been studied mostly in relation to birth defects, but several studies have related increased folate levels to the risk of preterm birth. There are plausible biological pathways by which folate levels could influence preterm birth (Scholl and Johnson, 2000). The empirical assessment of that relationship has generated mixed findings, with some evidence indicating that higher levels of folate reduce the risk of preterm birth (Savitz and Pastore, 1999; Scholl et al., 1996; Siega-Riz et al., 2004) and some evidence indicating that such an association does not exist (Czeizel et al., 1994; Savitz and Pastore, 1999; Shaw et al., 2004). A large randomized study reported that increased folate levels have a marginally positive effect in reducing the rate of preterm labor (Rolschau et al., 1999).

Isolated observational studies have addressed vitamin C levels and the risk of preterm birth, with some indication that low vitamin C levels are associated with an increased risk of premature rupture of membranes, leading to preterm birth (Siega-Riz et al., 2003). Increased levels of calcium have also been possibly associated with a reduced risk of preterm birth (Siega-Riz et al., 2003).

Zinc

The impact of zinc supplementation on fetal growth has also been studied. In a U.S. study of a low income population, Goldenberg and colleagues (1995) found an effect of supplementation on birth weight, such that mothers with a lower body mass index (BMI) who received supplementation had babies with greater birth weight than women with low BMI who did not receive supplementation. There was no difference among supplemented women with a higher BMI. With respect to studies examining preterm birth, evidence is conflicting (Castillo-Durán and Weisstaub, 2003; Caulfield et al., 1998; Merialdi et al., 2003; Villar et al., 2003a,b). Methodological limitations have hindered progress in this area and should be addressed by future research.

Fish and Fish Oil

A series of studies have addressed the hypothesis that the intake of larger amounts of the long-chain fatty acids found in certain fish might increase the duration of gestation and fetal growth (Olsen, 1993). Those studies were motivated by the relationship between prostaglandin levels and the timing of parturition and fetal growth. Investigators have compared aggregate populations who live in the Faroe Islands and Denmark, with one key difference between the two populations being the very high levels of intake of fish and whale by the population in the Faroe Islands. On average, the longer gestation times in the Faroe Islands contribute to the birth of infants born 100 grams heavier than infants in Denmark, and higher fetal growth rates contribute to infants who are 100 grams heavier. The n-3 fatty acids in erythrocytes were associated with an increased duration of gestation among Danish women but not among Faroese women (Olsen et al., 1986). One study of fish consumption and fetal growth (Olsen et al., 1990) found no overall relation between the frequency with which the mother ate fish and the duration of her pregnancy, but a positive association was found when the population was restricted to nonsmokers. A study with 965 pregnant Danish women for whom information on their levels of intake of n-3 fatty acids was available found no indication that the level of intake of n-3 fatty acids was associated with gestational duration, birth weight, or birth length (Olsen et al., 1995a). In an observational study conducted in the Faroe Islands, the levels of fatty acids in blood were examined as predictors of gestational age and birth weight (Grandjean et al., 2001). The levels of eicosapentanoic acid in serum were also found to be associated with an increased duration of gestation but a decreased birth weight for gestational length, which is a measure of the fetal growth rate. The report of seafood intake and pregnancy outcome in Denmark (Olsen and Secher, 2002) reported a rather strong but imprecise association between low levels of seafood consumption and the risk of preterm birth (odds ratio [OR] = 3.6; 95% confidence interval [CI] = 1.2–11.2).

Additional evidence of an association between fish oil consumption and an increased duration of gestation comes from randomized trials (Olsen et al., 1992). The investigators evaluated 533 pregnant Danish women who were divided into three groups: one group received fish oil, one group received olive oil, and one group received capsules with no oil. The gestational age distributions among these three groups of women varied at the time of delivery, with a shift toward prolonged gestation among the fish oil consumers; the group receiving no oil had gestation lengths that were intermediate among those of the three groups, and the group receiving olive oil had the shortest gestations. Comparison of the group receiving fish oil and the group receiving olive oil showed that gestations were 4 days longer and

the birth weight was 107 grams greater in the group receiving fish oil, with the apparent benefit derived from prolonged gestation and not from an increased rate of growth.

A multicenter trial involving 19 centers throughout Europe enrolled women with high-risk pregnancies (defined as a history of certain complications or adverse outcomes) or twin pregnancies (Olsen et al., 2000). Fish oil and olive oil were given to equal numbers of women in each arm of the trial. A notable protective effect against the recurrence of preterm birth was found, with an OR of 0.54 (95% CI 0.30–0.98), and fish oil was found to delay delivery across all centers involved in the trial.

Although randomized trials suggest a possible benefit of fish oil consumption on pregnancy duration, the information in the literature as a whole is not consistent in supporting a beneficial effect of seafood consumption and includes some indications of reduced growth rates, despite the prolonged gestation or the positive effects, which were limited to subgroups in the populations studied. This remains an active area of research, and both observational studies and randomized trials continue.

Employment

Employment during pregnancy has been of interest as a possible cause of increased risk of preterm birth for some time (Saurel-Cubizolles and Kaminski, 1986). The challenge of studying paid employment as an "exposure" is the many implications of work and the variability in the character of paid employment across geographic settings, time periods, and socioeconomic groups. Work has been conceptualized as a source of physical work demand, which is relatively rare in developed countries but which is common in many other parts of the world, or as a source of psychological stress because of its demands on the pregnant woman. In contrast, work is also a source and indicator of favorable socioeconomic circumstances; that is, the ability to have and maintain a job, the insurance benefits that employed women receive, and the psychological satisfaction resulting from certain types of jobs.

Recent studies have generally found no increased risk of preterm birth in association with employment per se but have provided suggestions that long work hours, physically demanding work, or other stressful conditions may be associated with an increased risk (see section below on Physical Activity). A large study across 16 European countries (Saurel-Cubizolles et al., 2004) found no association overall; but RRs for preterm birth on the order of 1.3 were found for women who work more than 42 hours per week, women who stand for more than 6 hours per day, and women with low levels of job satisfaction. However, a study of Thai women found that increased risks of small-for-gestational-age births but not preterm births

were associated with physically demanding work conditions (Tuntiseranee et al., 1998).

A more specific entity, premature rupture of membranes, was studied as a possible consequence of occupational fatigue, which was defined on a five-item scale that considered posture, work with industrial machines, physical exertion, mental stress, and environmental stress (Newman RB et al., 2001). Although these realms are diverse, each can be considered a work-related challenge, and in fact, a linear relationship between the number of sources of fatigue reported and the risk of premature rupture of membranes was observed, with an RR about 2.0 found among women reporting four or five sources of fatigue.

Given these and other findings, the continued study of employment-related physical activity and psychosocial stress offers an opportunity to study potential modifiable causes of preterm birth, but the consideration of paid employment in the aggregate in relation to preterm birth is unlikely to be helpful in identifying modifiable causes or improving the understanding of the causes of preterm birth more generally. The impact of employment is highly dependent on the socioeconomic conditions in the geographic location of the study, the implications of employment for economic resources and medical care access, and the particular character of the work. Given that heterogeneity, drawing inferences across studies of the impact of paid work is not possible.

Physical Activity

Evidence has found a clear pattern of a reduced risk of preterm birth in association with being employed generally compared with the risk in association with being unemployed (Saurel-Cubizolles and Kaminski, 1986; Savitz and Pastore, 1999; Savitz et al., 1990). However, among employed women, a number of reports suggest that jobs that require physical exertion may be associated with an increased risk of preterm birth (Mamelle et al., 1984; see the reviews of Berkowitz and Papiernik [1993] and Saurel-Cubizolles et al. [1991]). It is difficult to isolate the impact of physical exertion in the workplace from other aspects of employment, however. The key question is whether, among working women, physical activity on the job is associated with an increased risk of preterm birth, and here the evidence is distinctly mixed (Berkowitz and Papiernik, 1993; Savitz and Pastore, 1999; Shaw, 2003). Standing, lifting, and other measures of exertion, such as long work hours and the challenges of shift work, have been examined in a large number of studies, with modest and inconsistent associations with preterm birth detected (Ahlborg et al., 1990; Fortier et al., 1995; Xu et al., 1994). Among the candidate markers of physical work demands, none has emerged as the most important or the most promising

as having a causal influence on preterm birth on the basis of consistent empirical support for an association. The limited qualities of the assessments, the use of inconsistent definitions, and susceptibility to confounding may have blurred the findings for the association of interest. Nevertheless, despite the sizable number of studies that have evaluated whether such an association exists, there is as yet little basis for asserting that physical work is associated with an increased risk of preterm birth.

Leisure activities and their association with preterm birth have been of increasing interest in recent years. Historically, the primary concern was with an adverse effect of physical activity on fetal growth and the duration of gestation (Dye and Oldenettel, 1996). In more recent times, the focus has shifted toward the potential for a protective effect of being physically active on preterm birth (Sternfeld, 1997). Evidence suggests that the longer in pregnancy that exercise continues, the greater the reduction in the risk of preterm birth is (Evenson et al., 2002). Although intense activity has physiologic effects that raise concern over an increased risk of preterm birth, relevant mechanisms involving glucose metabolism and vascular effects would be consistent with a reduction in the risk of preterm birth.

Sexual Activity

The potential for adverse effects of sexual activity, particularly intercourse, during pregnancy has been of concern for some time due to the potential for direct effects of semen on initiating preterm labor, alteration of vaginal microflora, or other hypothesized pathways leading to preterm birth. Much of the interest and research on this question appeared in the 1980s, with consistent evidence that remaining sexually active during pregnancy was not associated with preterm birth (Klebanoff et al., 1984; Mills et al., 1981; Rayburn and Wilson, 1980). There was some suggestion that intercourse in the presence of certain infections; namely, *Trichomonas vaginalis* and *Mycoplasma hominis*, might increase risk for preterm birth (Read and Klebanoff, 1993), but more recent studies have continued to report not just an absence of increased risk associated with sexual activity but a notably diminished risk of preterm birth (Sayle et al., 2003). This may well be a reflection of selection for remaining sexually active, i.e., having a partner who may provide social support, having an absence of contraindications to remaining active, and the subjective sense of well-being that motivates continued activity.

Douching Before and During Pregnancy

A number of indirect lines of evidence suggest that the practice of vaginal douching might increase the risk of preterm birth. Douching is a com-

mon behavior and is more common among African American women than white women, consistent with the increased prevalence of bacterial vaginosis (BV) and preterm birth among African American women (Bruce et al., 2000). Furthermore, douching alters the vaginal microflora and may well facilitate the passage of vaginal pathogens to the upper reproductive tract, which contributes to inflammation and, possibly, to preterm birth. Few empirical evaluations of this hypothesis have been conducted thus far.

Women rarely douche during pregnancy, so the analyses have focused on douching during the period before pregnancy begins. Bruce et al. (2002) reported no association, after adjustment for confounders, between douching at any time before pregnancy and preterm birth, with ORs ranging from 0.7 to 1.1. However, among the small proportion of women who did report that they douched during pregnancy, the OR for preterm birth was 1.9 (95% CI 1.0–3.7). In another study (Fiscella et al., 2002), frequent and long durations of douching before pregnancy were found to be associated with an increased risk of preterm birth. Given the racial disparity in douching practices and the high degree of plausibility that douching influences pathways linked to preterm delivery, continued evaluations of the effects of this behavior are warranted.

PSYCHOSOCIAL FACTORS AND PRETERM BIRTH

In 1985 the Institute of Medicine (IOM) issued a report on low birth weight that concluded that stress was one promising avenue for future research (IOM, 1985). Since then, the findings of many more investigations have been published, as have numerous reviews, partial reviews, and commentaries on this area of research (Istvan, 1986; Kramer et al., 2001a; Lederman, 1986; Lobel, 1994; Paarlberg et al., 1995; Savitz and Pastore, 1999). However, existing reviews are outdated because of the burgeoning papers that have been published since the year 2000. This reflects the high level of scientific interest and public health attention to the topic of psychosocial factors and preterm delivery, especially research on stress and preterm delivery. This section summarizes the scientific findings on stress (including racism as a stressor), social support, and the intendedness of a pregnancy and their relation to the occurrence of preterm delivery.

Stress

Stress is defined as demands that tax or exceed the adaptive capacity of an organism and that result in psychological and biological changes (Cohen and Syme, 1985). This definition includes both environmental demands and the responses to them at multiple levels of analysis (cognitive, affective, immune, endocrine, cardiovascular, and so on). The breadth of this con-

struct has led to confusion among health care researchers and has muddled conceptual and measurement issues in the literature on stress and preterm delivery. Reframing stress as an umbrella concept (Lazarus and Folkman, 1984) that contains these distinguishable components has opened the way for stronger theory and research on stress and health in general (Cohen, 1995) and on birth outcomes more specifically (Lobel, 1994). Thus, this body of research can be divided by specific subtopics; namely, the effects of environmental demands, the effects of emotional and cognitive responses to those demands, and the role of biological stress responses such as hypothalamic pituitary axis (HPA) and cardiovascular and immune responses. Moreover, theoretical analyses have linked these distinct areas of empirical inquiry together into proposed pathways from the existence of stressors to the occurrence of preterm delivery (Hogue and Bremner, 2005; Holzman et al., 2001; Livingston et al., 2003; Lockwood, 1999; Rich-Edwards et al., 2005; Schulkin, 1999; Wadhwa, 2001).

The empirical research on stress and preterm delivery has become increasingly sophisticated in the past decade in several ways. First, the designs of observational studies have shifted from predominantly retrospective to predominantly prospective, measuring stress before rather than after delivery. Second, sample sizes are larger, in general, affording better power to test the effect(s) of interest. Third, the means of both the conceptualization and the measurement of stress have been strengthened. Fourth, most researchers now analyze data with attention to separating preterm labor and delivery from infant birth weight rather than studying only one of these outcomes without controlling for the other or lumping together several outcomes into what was sometimes termed "complications." Finally, studies have involved greater control for potential confounders of the stress-preterm birth relationship. Thus, the methodological problems that have plagued past research on stress and preterm delivery (Hoffman and Hatch, 1996; Lobel, 1994) are being ameliorated by trends in current research. Nonetheless, the findings of experimental studies that can provide firmer evidence for causality than observational studies are not yet available. Interventions in pregnancy that are aimed at reducing stress have generally used multifaceted treatment packages, including smoking cessation, support provision, prenatal education, and other ingredients, which prevents any conclusions of the effects of stress on preterm birth independent of the effects of other factors from being made (IOM, 2000). To date, prenatal intervention trials have not used state-of-the-art methodologies to isolate the effects of stress reduction from other psychosocial components; and none have examined the mediating processes involved to determine which components successfully reduced stress, which did not, or why (West and Aiken, 1997).

Although intervention trials on stress per se and preterm birth are absent or their findings are inconclusive, a handful of more rigorous observa-

tional studies on stressors (environmental demands) and preterm birth now exist. A second group of acceptable studies that have evaluated emotional, affective, or cognitive stress-related states and preterm birth exist. In addition, a number of notable animal and human studies on specific linkages between stress or emotion and various hypothesized mediators of preterm birth have been published. These mediators include BV (Culhane et al., 2001), cytokines (Coussons-Read et al., 2005), corticotropin-releasing hormone (Hobel et al., 1998; Lockwood, 1999; Mancuso et al., 2004), cortisol (Obel et al., 2005), blood pressure (McCubbin et al., 1996; Stancil et al., 2000), uterine artery resistance (Teixeira et al., 1999), and pregnancy-induced hypertension (Landsbergis and Hatch, 1996). This literature is discussed elsewhere in this report (Chapter 6). Finally, a small group of more recent studies has linked prenatal stress or emotion to a wide range of developmental outcomes, and both animal and human research in this area has been reviewed (Huizink et al., 2004; Schneider et al., 2002). The results have linked prenatal stress to outcomes ranging from fetal neurobehavioral indices (DiPietro et al., 2002; Wadhwa et al., 1996; also see the review by DiPietro [2005]) and fetal brain development (Graham et al., 1999; Hansen et al., 2000; Lou et al., 1994) to infant temperament and related infant outcomes (Huizink et al., 2002, 2003) and even some outcomes in toddlers (Laplante et al., 2004) and school age children (Rodriguez and Bohlin, 2005; Van Den Bergh and Marcoen, 2004; Van Den Bergh et al., 2005). Extensions of this work to the role of fetal stress programming in adult health outcomes are also capturing great interest (Barker, 1998; Huizink, 2005; Nathanielz, 1999).

Altogether these research developments strengthen the theoretical premises that causal pathways link maternal and fetal environmental stress exposures and maternal emotional states through biological mediators to preterm delivery or low birth weight and, furthermore, to developmental outcomes across the life span. However, the evidence to date is not sufficient or strong enough to draw firm conclusions on the many pieces of the complex and diverse pathways linking psychosocial factors to maternal and fetal outcomes. Nonetheless, it is possible to draw some tentative conclusions from recent research on the narrower topic of stressors or emotions as risk factors for preterm delivery. Much more intensive and rigorous scientific inquiry is needed before it will be known where, when, and how stress operates in pregnancy to influence developmental outcomes at any point in the life course (also see Chapter 6). Given the high levels of enthusiasm for research in this area, equal doses of objectivity, rigorous study, and the cautious drawing of conclusions on the effects of prenatal stress on distal outcomes are called for at this time.

This review begins where Savitz and Pastore (1999) ended their review of 20 methodologically acceptable studies. As they stated, the conclusions

that one can draw from that group of studies are hampered by methodological limitations, including retrospective study designs, sampling of special populations, small samples sizes, the use of various definitions of stress, the use of weak measures, and study enrollment often late in pregnancy. Nonetheless, the pattern of findings is informative. Of the 20 psychosocial studies reviewed, 11 studies assessed life events and tested the associations of those life events with preterm birth or gestational age. Of those 11 studies, 5 reported significant effects (Berkowitz and Kasl, 1983; Hedegaard et al., 1996; Mutale et al., 1991; Newton and Hunt, 1984; Newton et al., 1979), whereas 6 did not (Honnor et al., 1994; Lobel et al., 1992; MacDonald et al., 1992; Pagel et al., 1990; Stein et al., 1987; Wadhwa et al., 1993). Eleven studies assessed the associations of preterm birth and gestational age with anxiety, depression, or emotional distress. Of those 11 studies, 6 found significant effects (Copper et al., 1996; Hedegaard et al., 1993; Lobel et al., 1992; Orr and Miller, 1995; Steer et al., 1992; Wadhwa et al., 1993), whereas 5 did not (MacDonald et al., 1992; Molfese et al., 1987; Pagel et al., 1990; Perkin et al., 1993; Stein et al., 2000). In short, approximately half of the tests of stress measures and their association with preterm birth or gestational age outcomes were statistically significant.

Two notable early studies stand out because of their prospective designs and large sample sizes. In a sample of 5,873 Danish women, Hedegaard et al. (1996) found that experiencing one or more highly stressful life events at between 16 and 30 weeks of pregnancy was associated with a risk of preterm delivery (OR = 1.76). In an investigation of nearly 2,600 pregnant women in a large multisite U.S. study, Copper et al. (1996) reported that a two-item stress measure that assessed the extent to which women felt nervous, tense, and strained in general at 26 weeks of gestation predicted preterm birth, after controlling for race, age, marital status, insurance coverage, education, and substance use. Savitz and Pastore (1999) conclude that "psychosocial stress is among the more promising targets for [preterm birth] prevention strategies" (p. 93). This conclusion rests partly on the results of these stronger observational studies and also on specific criteria for interventions contained in the review, such as the modifiability of stress.

Studies published after the 1999 review continued to be somewhat methodologically uneven, but in general, research on stress and preterm birth has improved substantially since 1996 or 1997 in terms of the hypotheses and conceptualizations used, the measures used, sample sizes, and data analyses. Some of the newer studies are methodologically quite innovative. The IOM committee review of electronic databases yielded more than two dozen newly published reports on stress and its effects on preterm birth or birth weight. Databases containing data on low birth weight are viewed as potentially different, in terms of the mechanisms underlying the causes of

low birth weight, from those containing data on preterm births; but they are noted because of the substantial overlap of the two outcomes. Of 27 published reports, 21 were deemed of acceptable methodological quality for review and represent data from approximately 19 independent databases.[1] Many of the studies assessed multiple aspects of stress, such as major life events, anxiety, and depression. Of the 17 investigations (which evaluated data from 16 independent databases) that assessed any stress variables and that had preterm birth or gestational age as the outcome, only 2 obtained no significant findings. All four investigations on low birth weight that measured stress also found significant associations.[2] In sum, the overall pattern of findings since they were last reviewed suggests that more rigorous approaches are yielding more definitive results regarding the effects of stress on preterm delivery and gestational age, although the exact nature and strength of these effects are not yet clear. This led the committee to turn to examining the specific forms of stress involved, especially in more definitive studies, to obtain clues on the patterns of exposures.

Life Events

Life events are major events that individuals experience, such as divorce, a death in the family, illness, injury, or the loss of a job (Cohen et al., 1995). Eight studies assessed life events and tested whether a count of the number of events occurring during pregnancy or the severity or the impact of those events predicted preterm birth. Three obtained nonsignificant results, including one large prospective study (Goldenberg et al., 1996a), one prospective study with a small sample size (Lobel et al., 2000), and one analysis of a very large data set with data collected retrospectively (Lu and Chen, 2004). The other five studies all reported significant associations of some aspects of life events with preterm birth. In a large prospective study (in which maternal age, cohabitation, and education were controlled), Nordentoft et al. (1996) assessed life events at 20 weeks of gestation in a cohort of 2,432 Danish women and found that severe life events predicted preterm birth (adjusted OR = 1.14) but did not predict intrauterine growth restriction. Similarly, Dole and colleagues (2003) found an increased risk of preterm birth in women with negative-impact life events (RR = 1.8) in 1,962 pregnant women in North Carolina. Whitehead and colleagues (2002) analyzed two cohorts of women from a large study of 70,840 women in the

[1]In some cases, publications have addressed different issues within subgroups of the same database.

[2]Of the 6 studies deemed methodologically weaker than the original 21, 3 reported that stress had significant effects on preterm birth, gestational age, or birth weight.

United States (the Pregnancy Risk Assessment Monitoring System) by assessing life events 2 to 6 months after delivery (retrospectively). Experiencing more than two life events predicted preterm birth in primiparous pregnancies in one cohort (1994 and 1995), and more than five life events predicted preterm birth in multiparous pregnancies in the other cohort (1990 to 1993). Why these results did not cross replicate across cohorts is unclear (also see the findings of Lu and Chen [2004], based on a third cohort from the same study).

However, the results presented above are consistent with those of two additional studies restricted to African-American women. In one study, the number of prenatal major life events, as assessed prospectively, was associated with gestational age in a sample of 179 pregnant women selected from a larger data set (Parker Dominguez et al., 2005). The other study of African-American women (Collins et al., 1998), which had a case-control design, indicated that three or more life events in pregnancy were significantly associated (OR = 3.1) with very low birth weight (all cases were also preterm births; see also Sable and Wilkenson [2000]). Zambrana et al. (1999) also found a bivariate association between life events and gestational age in a large sample of women of Mexican origin or descent and African-American women studied in the second trimester. However, the strongest effect in that study was detected when life events were combined with other stress measures into a latent factor in a multivariate model.

Thus, there is some consistent evidence that major life events are associated with preterm birth, although the evidence is by no means uniform. High numbers of life events and severe life events or life events with the greatest impact have been more consistently predictive of preterm birth across studies.[3] On the whole, the focus in the future should be on approaches to the study of life events that delineate events by their severity and emphasize those with the highest negative impacts.

Chronic and Catastrophic Stress Exposures

A second set of studies involved a common chronic stressor, such as being imprisoned (Hollander, 2005) or homeless (Stein et al., 2000) during pregnancy or experiencing a catastrophic event occurring during pregnancy (Glynn et al., 2001; Lederman et al., 2004). For example, Lederman and colleagues (2004) assessed the impact of the time of gestation at the time of the World Trade Center terrorist attack on September 11, 2001, among

[3]One exception is the finding of Goldenberg et al. (1996a) that a low frequency of positive life events during pregnancy was weakly associated with preterm birth.

300 nonsmoking women in New York City who were pregnant at the time. Women who were in the first trimester at the time of the attack delivered infants of significantly shorter gestations, and women whose place of employment was within 2 miles of the World Trade Center had marginally shorter gestations. Strikingly similar effects were found by Glynn and colleagues (2001), who examined gestational age at delivery of 40 women who experienced a major earthquake in the first, second, or third trimester or postpartum. They found a significant effect of the timing of the earthquake during pregnancy on gestational age, such that the later in pregnancy that an earthquake occurred, the longer the gestation was. The longest gestational age in that study was among women who had already delivered at the time of the event (and who were effectively unexposed), and the shortest gestation was among women who experienced the earthquake in the first trimester. Although the sample size was small and some alternative explanations cannot be ruled out, these results are intriguing, especially because of their similarity to those of Lederman et al. (2004), as they indicate that the timing of sudden traumatic environmental stressors during pregnancy may affect the timing of delivery. Although the methodological strengths of these studies vary, they avoid some of the pitfalls encountered in life events approaches because all the participants in the studies experienced the same stressor.[4]

Turning to more chronic forms of exposure, Stein et al. (2000) studied 237 homeless women interviewed at 78 shelters or meal programs. The severity of homelessness, especially the variable of the percentage of the woman's lifetime that she had been homeless, predicted both preterm birth and low birth weight (each of which controlled for the other). The analyses controlled for many other variables, such as substance use, trauma and distress, prior birth complications, race-ethnicity, income, and various medical risk factors. The severity of homelessness is a fairly objective measure of chronic stress or strain and not merely a measure of perceived stress or distress; but it may have been confounded nonetheless by inadequate nutrition or general health neglect, as the authors point out, which could account in part for these effects. Nonetheless, these are unique findings on the possible role of chronic stress in preterm birth and low birth weight.

Misra and colleagues (2001) also retrospectively studied chronic stress during pregnancy in 739 low-income African-American non-Hispanic women interviewed after delivery. Multivariate analyses indicated that chronic stress predicted preterm delivery (adjusted OR = 1.86) when several

[4]See also earlier studies by Kuvacic et al. (1996) on the effects of expatriation on preterm birth and Levi et al. (1989) on the effects of the Chernobyl nuclear disaster on preterm birth.

biomedical and other psychosocial factors were controlled for. The chronic stress measures contained 12 items that assessed financial, family, work, health, and other forms of ongoing stress.

In sum, studies of chronic and catastrophic stress exposures are suggestive of an association between stress and preterm birth, although the findings are not yet definitive. Such studies offer an opportunity to use quasiexperimental designs instead of correlational designs, and these quasiexperimental studies may add to the ability to draw inferences (Cook and Campbell, 1979; Shaddish et al., 2002), and also have the potential to test competing theories about acute versus chronic stress exposures and their effects on preterm birth.

Emotional Responses and Affective States

Anxiety

The early research on psychosocial risk factors for preterm delivery and low birth weight focused on maternal anxiety (Gorsuch and Key, 1974). Other studies over the years have focused on the role of general distress. Determination of whether either depression or anxiety is a risk factor for preterm delivery has, however, been difficult for many reasons. Among these is the fact that the two emotional states are often comorbid, although they are distinguishable clinically. However, the questionnaire measures used in obstetric research to assess anxiety and depression are not well suited to their differentiation. Thus, many studies have investigated general distress by using the General Health Questionnaire (Hedegaard et al., 1993, 1996; Perkin et al., 1993) or the Hopkins Symptom Checklist (Paarlberg et al., 1996). General emotional distress may not be as clear-cut a risk factor as the potentially separable effects of either anxiety or depression.

Recent studies suggest that anxiety may be a potentially important risk factor for preterm delivery. The IOM committee found 12 studies in total that tested the emotional components of stress as predictors of preterm birth. Eleven studies had prospective designs; of these, nine tested the association of anxiety with gestational age or preterm birth. Two found no significant effects for state anxiety (Lobel et al., 2000; Peacock et al., 1995); one study found that general anxiety was associated with intrauterine growth restriction (but not with preterm birth), but only in white patients (Goldenberg et al., 1996a); and one study found that general anxiety was associated with preterm labor in women who had a history of preterm labor (Dayan et al., 2002).

Four more investigations were very consistent in finding that anxiety concerning the pregnancy itself was associated with gestational age or preterm birth. For example, Rini et al. (1999) reported that prenatal anxi-

ety (a combination of state anxiety and pregnancy anxiety), assessed by interviews with women at 28 to 30 weeks of gestation, was associated with gestational age in 230 Hispanic and white women when other sociodemographic, medical, and behavioral risk factors were controlled for (estimated OR for preterm birth = 1.59). In a larger prospective study, Dole et al. (2003) replicated these findings; pregnancy-related anxiety at 24 to 29 weeks of gestation predicted preterm birth in a sample of 1,962 women (RR = 2.1) when the data were adjusted for alcohol and tobacco use. This effect was robust for women with spontaneous preterm labor rather than the medical induction of labor, with medical comorbidities controlled for, and was a stronger effect than that of the life events noted above.

Mancuso and colleagues (2004) also replicated these findings with a sample of 282 women assessed twice during their pregnancies (Behavior in Pregnancy Study [BIPS]). Pregnancy-specific anxiety at 28 to 30 weeks of gestation (but not at 18 to 24 weeks of gestation) significantly predicted gestational age. In addition, Mancuso et al. (2004) reported that corticotropin-releasing hormone levels mediated the effects of pregnancy anxiety on gestational age (see also Hobel et al. [1999]). Further multivariate analyses of this sample reported by Roesch et al. (2004) sought to determine which of three stress indicators (state anxiety, pregnancy anxiety, and perceived stress) was most predictive of gestational age in the women participating in BIPS. They determined that pregnancy anxiety was the only significant predictor of gestational age when all three indicators were included in the model. Other studies of perceived stress that used the standard scale in BIPS (PSS) have had mixed results for this component (Lobel et al., 1992, 2000; Sable and Wilkenson, 2000; Zambrana et al., 1999).

When considered together, these results are quite consistent in pointing to anxiety as a possible risk factor. Although results of studies on general anxiety are somewhat mixed, studies on anxiety regarding the pregnancy itself are more consistent in predicting gestational age at birth or preterm birth. The most vulnerable times in pregnancy for emotions to have effects on physiology are not yet clear, but some research points to weeks 24 and 30 of gestation (Rini et al., 1999). The possibility of the confounding of anxiety over existing medical risk conditions was considered and controlled to some extent in some of these investigations, suggesting that anxiety over existing medical risk conditions does not fully account for the effects. That is, high-risk pregnancies may elicit anxiety, but this does not appear to account for these findings; in short, anxiety resulting from knowledge of one's medical risk conditions is not implicated as a risk factor per se. Follow-up research on anxiety and its timing and mechanisms of effects on preterm labor and delivery is recommended.

Depression

Ten studies on depression and preterm birth or low birth weight were reviewed. All studies had prospective designs. Of these, four reported nonsignificant effects (Dole et al., 2003; Goldenberg et al., 1996a; Lobel et al., 2000; Misra et al., 2001; Peacock et al., 1995). Three found that prenatal depression in the mother affected fetal growth (Hoffman and Hatch, 2000) and birth weight percentiles (Paarlberg et al., 1999). Two studies reported associations of depression and preterm delivery (Dayan et al., 2002; Jesse et al., 2003; Orr et al., 2002). One found significant effects only among women who were underweight (BMI < 19) before the pregnancy (Dayan et al., 2002). Another was a large study of African American women only (Orr et al., 2002) reporting adjusted OR of 1.96 for spontaneous preterm birth among women in the top 10 percent on a standard depression measure.

Overall, recent prospective studies on depression do not suggest a strong pattern for depression as a general risk for preterm delivery consistent with the results of earlier studies (Copper et al., 1996; Perkin et al., 1993) with some exceptions. For example, depression in African American women seems to be an area worthy of further investigation. Effects of depression on birth weight or fetal growth is also inconsistent but there are some indications that depression may be a risk factor for fetal growth or low birth weight. Further research is needed to clarify this topic of research. Pathways from emotion to low birth weight through health behaviors such as diet and nutrition, substance use, sleep, and inactivity are important to elucidate. Women who are depressed or anxious during pregnancy are unlikely to take care of themselves as adequately as those who are not. Anxiety may be linked to different behavioral implications than depression. Studies of these states also must address their frequent confounding as well. This is a potential topic for follow-up research.

Other Forms of Stress Exposure

A relatively small number of studies have assessed the effects of daily stressors on preterm birth but have shown nonsignificant results (Paarlberg et al., 1996; Wadhwa et al., 1993). It is possible that these measures do not capture levels of stress exposure high enough to influence pathways to prematurity. Although daily stressors may operate in combination with other stress exposures, such as major life events, and interact with responses such as anxiety or depression to contribute to the risk of preterm birth, they do not seem promising overall for predictive purposes.

Two other bodies of research are relevant to the role of stress and preterm delivery. One is on the effects of occupational or work stress on preterm delivery (Woo, 1997). This area is related to but distinct from

the topics of physical activity and employment discussed earlier in this chapter. Whether or not a woman is employed, she may engage in various degrees of daily physical activity or strain, but only women who are employed would potentially experience occupational stress. Savitz and Pastore (1999) highlighted previous studies on occupational stress and preterm birth that were consistent in showing significant associations of either occupational stress or physical strain with preterm labor or delivery (Brandt and Nielsen, 1992; Brett et al., 1997; Henriksen et al., 1994; Homer et al., 1990). In a related study, Pritchard and Teo (1994) found that assessments of household strain were significant predictors of preterm birth in 393 Swedish women.

This area is complex because it has sometimes been framed as an issue of whether employment during pregnancy is itself risky or whether the characteristics of a woman's employment are the preterm birth risk-associated factor. Key issues include the type of work activities, the number of hours of work each day or week, the time during pregnancy when a woman works, the work environment, and the psychological strain (cognitive and emotional) that may be associated with work. When these factors are quantified, it may be found that some employed women are at risk and others are not. This is another topic worthy of future investigation.

A second area relevant to stress is that on exposure to personal violence. A small but growing body of work suggests that women who experience domestic or personal violence during pregnancy are at risk for adverse birth outcomes (Amaro et al., 1990; Coker et al., 2004; Parker et al., 1994a; Rich-Edwards et al., 2001; Shumway et al., 1999). The extent to which this is the result of stress processes rather than other mediating processes is unclear, however. In addition, most studies appear to view domestic or personal violence as a chronic stressor and have observed that violence affects birth weight but not preterm birth.

Mechanisms Linking Stress and Emotions to Preterm Birth

Maternal stress can cause the release of increased levels of catecholamines and cortisol, which could prematurely activate placental corticotropin-releasing hormone, thereby precipitating the biological cascade leading to the onset of preterm labor (see Chapter 6). Stress can also alter immune function, leading to increased susceptibility to intra-amniotic infection or inflammation (Wadhwa et al., 2001). Additionally, stress may induce high-risk behaviors as a means of coping with stress (Whitehead et al., 2003).
Evidence is also accumulating that infections may play a key role in the pathogenesis of preterm birth, particularly very preterm delivery (see Chapter 6). Although researchers have recently focused on bacterial vaginosis (BV), several other infections, including asymptomatic bacteriuria, sexually transmitted infections, and periodontal infections, have all been implicated.

There is a need for investigation of the specific pathways whereby distinct stress and emotional and affective factors contribute to preterm birth. Past research provides some clues to possible avenues of investigation. For example, maternal anxiety has been implicated more in early labor and delivery via HPA pathways, whereas depression has been associated with poor health behaviors and their consequences for fetal growth. In particular, greater theoretical analysis of the intensity and duration of distinct emotional states such as anxiety and depression and their consequences for pregnancy outcomes, such as spontaneous preterm labor, spontaneous rupture of membranes, and fetal growth restriction, is needed. (See Chapter 6 for a more extensive review and discussion of the pathways from stress to preterm birth.)

More specifically, the role of anxiety in the preterm pathogenesis process has not been adequately evaluated (Kurki et al., 2000; McCool et al., 1994). One notion, built on common anecdotes, is that a single episode of strong emotion, such as anxiety from being in New York City when the World Trade Center was attacked, in New Orleans during Hurricane Katrina, or in Los Angeles during the Northridge Earthquake, can precipitate early labor. A second possibility is that a chronic state of anxiety resulting from a clinically diagnosable anxiety disorder or subclinical set of symptoms places a woman at risk for preterm delivery. A third possibility is that a combination of the first two possibilities, in the form of an anxious disposition combined with a highly stressful acute event or series of events, may interact to cause early labor.

Limiting the inquiry to the role of anxiety and its biological consequences may prove more fruitful than earlier and cruder approaches to studying general distress and its influence on preterm delivery. Earlier, such studies served the field well in identifying potentially new risk factors, but more scientific precision on the emotional experience of pregnancy and its consequences is greatly needed now to obtain a further understanding of the association of stress with preterm delivery. For example, emerging research indicates that physiologic stress reactivity (e.g., endocrine and cardiovascular) decreases across gestation (de Weerth and Buitelaar, 2005; Glynn et al., 2001, 2004; Matthews and Rodin, 1992; Schulte et al., 1990), which has substantive implications for the role of psychosocial factors as both risk factors and targets for intervention.

Culture, Race, Ethnicity, and Stress

A complication of research on stress in general and on emotional states during pregnancy more specifically is that emotional experience and responses to emotion are at least partially culturally grounded (Mesquita and Frijda, 1992). That is, people of different cultures differ in their comprehension of and ability to accept the expression of emotions, such as anxiety and

sadness. In some subgroups in the United States, the expression of anxiety may be much more normative and accepted than in others, in which it may be frowned upon, misunderstood, or ignored. Languages may also differ in their abilities to translate the word "stress." The Spanish language, for example, does not have a specific translation for the word "stress." Anxiety, or *nervios*, is understood in Spanish, whereas stress in general is not. Thus, studies of stress as a risk factor by the use of standard scale assessments delivered in Spanish may or may not be assessing the same phenomenon that these scales assess when they are delivered in English. This poses a special challenge to researchers.

Similarly, African American women, whose rates of preterm delivery and infant mortality are the highest in the United States, have unique experiences of stress, yet there is a dearth of studies on African American cultural factors pertaining to stress, emotion, or pregnancy. Parker Dominguez and colleagues (2005) found that neither anxiety nor perceived stress was significantly correlated with gestational age or low birthweight among 179 pregnant African American women. Instead, a newer measure of the extent to which women experienced intrusive thoughts or rumination about their two most severe major life events was associated with lower birth weight when gestational age in linear multiple regression analyses was controlled for. Intrusive thought is a recognized symptom of trauma containing both cognitive and emotional components (and is often symptomatic of posttraumatic stress disorder).

The possibility that low-income African American women experience more symptoms of trauma and that these are more important risk factors for preterm birth than depression or anxiety for this or other groups is intriguing. More generally, researchers must address the possibility that the same aspects of stress may not pose a risk for preterm birth in the same manner for all racial and ethnic groups. In-depth studies of specific racial-ethnic and cultural groups that include culturally specific stress measures may yield answers to whether stress is a risk factor for preterm birth for specific groups. The answers may be more complex than has been imagined. Anxiety may be a stronger risk factor for Latinos and whites, whereas depression, posttraumatic stress disorder, or racial stressors may be more potent individual-level risk factors for African American women. These possibilities might help to explain why research on stress and pregnancy outcomes has yielded equivocal findings and also why the findings from studies in foreign countries with more homogeneous populations, such as Denmark, have been more definitive. Furthermore, these possibilities suggest very different intervention strategies for different racial and ethnic groups (Norbeck and Anderson, 1989).

Racism

The pressing need to reduce the racial disparities in infant mortality, low birth weight, and preterm birth in the United States has led to new theories and new research directions on the pregnancies of African-American women (Hogue and Vasquez, 2002; Rich-Edwards et al., 2001; Rowley, 1994, 2001; Rowley et al., 1993). In particular, attention is being directed to the role of racism and discrimination in health outcomes in general (Krieger, 2000) and in pregnancy outcomes specifically (Collins et al., 2000, 2004). Racism is defined as racially motivated interpersonal and institutional discrimination (Krieger, 2000). Several research teams have developed self-report measures of racism, and these measures have been used in a handful of case-control and prospective studies of pregnancy. Collins and colleagues (2000) published the first study on this issue with a sample of low-income African American women in Chicago who delivered very low birth weight infants (n = 25), all of which were preterm, or matched controls with infants of normal birth weight (n = 60). They used Krieger's measures developed for the CARDIA study (Krieger, 1990; Krieger and Sidney, 1996). These measures query participants about their experiences of racism at work, at school, when getting medical care, when receiving service at stores or restaurants, and when finding housing. Mothers with infants with very low birth weights were twice as likely to report experiences of racial discrimination during pregnancy as women who delivered infants of normal birth weight. After adjustment for socioeconomic condition, levels of social support, cigarette smoking, alcohol intake, and illegal drug use, the adjusted OR was 3.2.

Four subsequent studies have been published since publication of the first one by Collins et al. (2000), two of which had case-control designs (Collins et al., 2004; Rosenberg, 1965) and two of which had prospective designs (Dole et al., 2003; Mustillo et al., 2004). Mustillo and colleagues (2004) examined racial discrimination using the CARDIA data set, which included data from a 10-year prospective study of a large cohort of African American and white men and women. Their sample comprised the 352 African American and white women who gave birth to live infants at 20 weeks gestation or longer. Racism was measured by use of the Krieger measure at year 7 of the study, and low birth weight for an intervening pregnancy was assessed by self-report at year 10. Several findings are of interest. First, race was a risk factor for preterm birth, as expected (OR = 2.54); but the risk estimate was reduced after adjustment for lifetime experiences of racism, suggesting that racism may mediate the racial-ethnic difference in preterm birth rates. Smoking, alcohol intake, depression, and the amount of weight gained during pregnancy did not have such effects. Second, women who had experienced lifetime discrimination were nearly five times more

likely to deliver a low birth weight infant than those who had not experienced racism. This relationship was reduced by including preterm birth in the model, suggesting that the effect of discrimination on birth weight was as a result of the effects of racism on the likelihood of an earlier delivery. Thus, lifetime experiences of racism explained the racial and ethnic disparities in the rates of both preterm birth and low birth weight.

Collins and colleagues (2004) also considered lifetime exposure to racism as well as pregnancy exposure in a case-control study of 104 African American women in Chicago who delivered very low birth weight preterm infants and 208 matched controls who delivered normal birth weight infants. Lifetime exposure to racial discrimination in three or more domains of life was associated with very low birth weight (OR = 3.2; OR = 2.6 adjusted for age, education, and cigarette smoking). The outcomes were not associated with perceived prenatal racial discrimination. The authors conducted post hoc tests, whose results suggested that the effects detected were not attributable to recall bias because of infant illness among the low birth weight infants. In addition, the strongest risk was for college-educated African American women. Collins and colleagues (2004) conclude that "lifelong accumulated experiences of racial discrimination by African American women constitute an independent risk factor for preterm delivery" (p. 2132). One apparent pathway whereby racism appears to influence health and possibly prenatal processes is by cardiovascular functioning (Krieger, 1990; Krieger and Sidney, 1996). (For a complete review of the literature on racial and ethnic disparities in pregnancy outcomes, definitions and measures of racism, the conceptualization of racism as stress, and findings, see the work of Giscombe and Lobel [2005]).

The following are key questions to be resolved in future research: Is racism a risk factor for preterm birth or fetal growth restriction or both, and, if so, by what pathways? Does racism act in association with other factors, such as social class, age, medical risk factors, or other stress or emotional factors to pose a risk? If racism is a potent risk factor, are there effective, practical, and cost-effective ways to mitigate its effects on maternal and infant outcomes?

In general, the emerging literature on racism and preterm delivery suggests that racism may be a potent stressor throughout the lifetimes of African American women that contributes to an explanation of the racial and ethnic disparities in the rates of both preterm birth and low birth weight. However, further study is needed to replicate and extend the existing studies. One challenge researchers face is the difficulty of assessing experiences of racism. Many factors contribute to underreporting of the experience. This challenge requires further precise work by investigators in future.

Social Support

The term *social support* incorporates research on social integration, social networks, and social support (House et al., 1988). The last element (social support per se) has been studied mainly as a perception that others will provide the mother with specific resources during pregnancy if she should need them (Sarason et al., 1987). Alternatively, social support refers to a set of interactions or exchanges with others in which emotional concern, instrumental aid, or information about the environment or one's self are provided (House, 1981). *Instrumental aid* includes task assistance and material aid. *Emotional concern* includes affection, opportunities to express feelings, and empathy and understanding. *Information* includes constructive feedback, validation, advice, and guidance. For the purposes of this report, all of these conceptualizations (social integration, network characteristics, perceived available support, and actual receipt of support) and their associated measures are relevant.

In the small body of observational research on preterm delivery, many different ways of defining and measuring social support have been adopted, with, for the most part, no consensus or overlap across studies. Not surprisingly, intervention research has focused on the actual provision of support during pregnancy. Support may be provided by professionals, paraprofessionals, other pregnant women, family members, friends, or a woman's partner. The majority of past intervention research has been on the professional or paraprofessional support provided by telephone calls, by home visits, or in prenatal care settings. In contrast, observational research has been slanted toward family or partner support. Notably, the specific sources of support that women of different subgroups use differ by their racial-ethnic, cultural, and sociodemographic backgrounds (Dunkel-Schetter, 1998). For some groups, the baby's father may be the most important source, whereas for other groups, the pregnant woman's mother or family may be her most likely source of support (Sagrestano et al., 1999).

Observational Studies

Early observational studies drew attention to the possibility that prenatal social support might reduce the incidence of adverse outcomes either directly or as a result of their ability to buffer the effects of stress (see the reviews by Brooks-Gunn [1991], Dunkel-Schetter [1998], and Oakley [1988]). However, early research on psychosocial factors and birth outcomes tended to lump together distinct factors such as stress and social support (Nuckolls et al., 1972) and to combine distinct outcomes such as preterm birth and low birth weight into one category of complications (Boyce et al., 1985, 1986; Norbeck and Tilden, 1983).

The next set of observational studies corrected for some of these problems but did not confirm the direct link between social support and gestational age or preterm birth (Molfese et al., 1987; Pagel et al., 1990; Reeb et al., 1987), although associations were detected in some specific racial-ethnic groups (Berkowitz and Kasl, 1983; Norbeck and Anderson, 1989). These studies were followed by another generation of studies (after 1990) involving larger sample sizes, improved study designs (prospective), better measures, and more carefully controlled analyses. The results of these studies were highly consistent: virtually every study found significant associations between social support variables and birth weight or fetal growth (Buka et al., 2003; Collins et al., 1993; Feldman et al., 2000; Mutale et al., 1991; Pryor et al., 2003; Turner et al., 1990). However, those that tested for an association between social support variables and preterm labor or delivery specifically found no evidence that such a relationship exists (Dole et al., 2003; Feldman et al., 2000; Misra et al., 2001).

Thus, the results of observational studies over two decades do not confirm the hypothesized correlation between social support and preterm delivery, but they do provide fairly consistent evidence for a direct association between prenatal maternal social support and infant birth weight. The magnitude of this effect is difficult to determine from existing research.

Intervention Research

Enthusiasm for the theoretical premise that the provision of social support to pregnant women could reduce adverse pregnancy outcomes fueled a handful of controlled intervention studies published in the late 1980s and 1990s (Heins et al., 1990; Oakley et al., 1990; Olds et al., 1986; Rothberg and Lits, 1991; Spencer et al., 1989). Some of these combined social support with other programmatic elements, such as nutrition or smoking cessation interventions. Many aimed to reduce adverse pregnancy outcomes overall, including both low birth weight and preterm birth, in a composite outcome variable. These intervention studies have been extensively reviewed elsewhere (Blondel, 1998; Elbourne and Oakley, 1991; Elbourne et al., 1989; Olds and Kitzman, 1993). In 1999, Goldenberg and Rouse concluded their review as follows: "there is little evidence to support the belief that a significant reduction in preterm birth can be achieved through the systematic provision of psychosocial support" (Goldenberg and Rouse, 1999, p. 114).

A recent Cochrane review that used meta-analytic techniques systematically evaluated 16 trials involving 13,651 women in total (Hodnett and Fredericks, 2003). The study design used randomization to the treatment and the control groups, and additional support was provided to women in the treatment group in the first or second trimester if they were at risk of

preterm delivery or fetal growth restriction. The interventions included standardized or individualized programs that were provided on several occasions in home visits by midwives, nurses, or social workers; during regular antenatal clinic visits; or by telephone. Meta-analyses revealed that overall these interventions were not associated with reductions in the rates of preterm birth (11 trials) or low birth weight (13 trials). The authors concluded that the provision of additional support did not reduce the likelihood of giving birth too early or of delivering an infant who was smaller than expected (Hodnett and Fredericks, 2003). These conclusions are consistent with those of another recent review (Lu et al., 2005), in which it was found that only 1 of 12 randomized controlled trials of the provision of psychosocial resources to reduce low birth weight was effective (Norbeck et al., 1996). However, some of the randomized controlled trials showed that the provision of psychosocial resources affected a range of other outcomes, such as anxiety, satisfaction with care, awareness and knowledge of risk conditions, perceived mastery, and engagement of the mother in health-promoting behaviors (Klerman et al., 2001).

The inability of intervention trials to demonstrate the effects of social support on either preterm birth or low birth weight is puzzling to experts and is in some ways a source of controversy. Although study designs can always be improved, the high degree of consistency of the results across numerous trials, combined with the fact that at least some of the studies were quite rigorous, tends to refute the possibility that the studies had general design flaws or methodological explanations as the sole reason for the lack of demonstration of an effect of social support. A more specific possibility raised by Hodnett and Fredericks (2003), however, is that the ability to identify women at high risk of delivering infants preterm or of low birth weight is so imprecise that many women in these trials were not actually at higher risk.

The identification of women at high risk of preterm birth might be improved; and with greater understanding of the etiology of preterm birth and with the availability of better indicators of risk, greater precision in targeting the subset(s) of pregnant women who could benefit from supportive interventions of specific kinds may be achieved. Lu et al. (2005) echo this sentiment, pointing out that most trials do not have effective risk screening procedures; only 2 of the 12 trials that they reviewed even evaluated the effectiveness of their risk screening procedures for the untreated group. Moreover, in some studies, the risk factors did not predict outcomes for the untreated study participants, as would be expected. If investigators are not successfully targeting selected risk groups, then the trials are not likely to have expected effects.

In addition, it has been pointed out that the treatments must be much better matched to the risk factors (Lu et al., 2005; Olds and Kitzman, 1993).

Norbeck et al. (1996), for example, selected pregnant women for intervention partly on the basis of inadequate social support, and then provided social support to those in the treatment group, which produced a reduction in the numbers of infants born with low birth weights. Thus, because of limitations in risk screening and intervention matching, the matter of whether supportive interventions of some kinds might reduce the rates of preterm birth for at least a subset of women has probably not yet been adequately tested.

A further concern is the absence of a strong theoretical basis for support intervention trials. For example, only 5 of 12 of the studies reviewed by Lu et al. (2005) had a predictive model on which the intervention was based. Contributing to this concern is the fact that, despite the large number of experimental trials, the causal mechanisms that might underlie a relationship between low levels of social support and early labor or delivery have not been specified. Research indicating that social support is associated with various demographic factors, better health behaviors, more optimal prenatal care, and greater wantedness of the pregnancy may be informative about the pathways linking social support to fetal growth.

Interestingly, considerable theoretical findings on the association of social support and health more broadly are available, but these have not been applied in a significant way to the study of pregnancy (Cohen, 1988; Cohen and Syme, 1985; Taylor, 2006). Furthermore, little has been culled from the available rigorous research and theory on social support interventions for other medical conditions (Cohen, 2000), such as cancer (Helgeson and Cohen, 1996). Drawing from what is known about how to conceptualize, assess, administer, and evaluate support resources in other populations requiring health care may provide new perspectives on how to do so for pregnant women.

A final possibility raised by Hodnett and Fredericks (2003) is that no matter how much or how effective social support is, it may not be sufficiently powerful to improve substantially the outcomes of pregnancy, especially given the long-standing conditions of social deprivation endured by the women at the highest risk. This possibility must be considered in the case of preterm birth, for which neither observational research nor randomized controlled trials have offered any empirical basis for further research and plausible theoretical mechanisms are lacking.

Personal Resources

The emerging literature on personal resources warrants attention in multilevel research attempts to understand preterm birth better. The term *personal resources* refers to individual differences in views about one's self and the world, such as self-esteem, mastery, perceived control, and opti-

mism. These are conceptualized as relatively stable characteristics of individuals that are generally protective of the individual's health and that function as coping resources (Lachman and Weaver, 1998; Thoits, 1995). They can be more broadly conceptualized as resilience resources, along with social support and other values, beliefs, and personality traits, which function similarly. Studies to date on personal resources and preterm birth have shown some interesting results. In a prospective study of 553 nulliparous African American pregnant women at less than 26 weeks of gestation, Edwards et al. (1994) found that two specific questions from a standard self-esteem measure predicted gestational age and preterm birth, and one item predicted infant head circumference. Jesse et al. (2003) found that the same standard self-esteem measure predicted a lower risk of preterm birth (RR = 0.865) in 120 pregnant women studied at 16 to 28 weeks of gestation, but that the effect became marginally significant when other variables were controlled for in the analyses. Rini et al. (1999), using the same standard measure used by Jesse et al. (2003), combined with standard scales of mastery and optimism into a broader personal resources factor, reported that self-esteem again predicted birth weight but not gestational age in more than 200 pregnant women assessed in midpregnancy. The findings of these studies are contradictory as to whether self-esteem influences preterm birth independently of birth weight. In addition, there is little discussion in the literature of the mechanisms by which such an effect would occur. It is possible that women with higher levels of self-esteem take better care of themselves during pregnancy, which has plausible pathways to fetal growth and to the use of health care for the management of risk factors for preterm birth and intrauterine growth restriction. However, these pathways remain to be fully explicated and tested.

Other pertinent studies have evaluated mastery, which is a sense of efficacy over one's environment (Copper et al., 1996), and dispositional optimism, which refers to expectations for positive life outcomes in future (Lobel et al., 2000). In general, however, those studies did not find an association of these factors with preterm birth (see also the work by Rini et al. [1999]). However, Misra et al. (2001) report that locus of control was an independent predictor of preterm birth (unadjusted OR = 2.22; adjusted OR = 1.75 after controlling for biomedical factors). Women who perceived that they could influence the health of their children at birth had lower rates of preterm birth.

In sum, the few available studies on self-esteem, mastery, optimism, and perceived control in women expecting infants do not consistently predict preterm birth. It may be that these factors are more related to fetal growth and low birth weight or that these factors are more relevant to particular subgroups of pregnant women, such as populations of women who are socioeconomically disadvantaged. There is a need for the develop-

ment of hypothesized pathways to preterm birth as a basis for any future study of these factors. In addition, the study of these factors in combination with social factors, such as race and ethnicity, social class, and neighborhood factors (see Chapter 4), is recommended.

Intendedness of Pregnancy and Preterm Delivery

The term *unintended* refers to those pregnancies that are unwanted or mistimed (i.e., they occur earlier than desired by the parents). Intentions are measured by self-report by using standard survey questions that can distinguish between whether the woman wanted a child now, not now but at some point (mistimed), or not at all (unwanted). These questions are answered after conception and in many studies are answered after delivery, which may introduce retrospective bias.

It is estimated that approximately 60 percent of all pregnancies are unintended, and of these, about half end in a live birth (IOM, 1995). Women with unintended pregnancies are less likely to seek early prenatal care (Bitto et al., 1997; IOM, 1995; Kost et al., 1998; Pagnini and Reichman, 2000) and are more likely to use alcohol or tobacco (IOM, 1995). They also appear to be more likely to experience high levels of exposure to psychosocial stress and depressive symptoms (Orr and Miller, 1997). Although unintended pregnancies occur among women across the sociodemographic spectrum, they are disproportionately likely among mothers who are adolescent, unmarried, or over age 40 (Bitto et al., 1997; IOM, 1995). The child of an unwanted pregnancy (as opposed to the child of a wanted or a mistimed pregnancy) is at greater risk of low birth weight, death in the first year of life, abuse, and receiving insufficient resources for optimal early child development (IOM, 1995). Additional consequences occur for the parents of unwanted pregnancies. For example, a study that used data from the Pregnancy Risk Assessment Monitoring System database of 39,348 women in 14 states who delivered a live-born infant (Goodwin et al., 2000) found that women with unintended pregnancies had a 2.5 times greater risk of physical abuse.

Having an unintended pregnancy is estimated to increase the odds of delivering an infant of low birth weight by about 1.2 to 1.8 (IOM, 1995). However, only three studies on intentions and preterm birth were available as of 1995, and of those three studies, two were unpublished. On the basis of the findings from these preliminary studies, IOM (1995) indicated that the increased risk of low birth weight because of an unintended pregnancy appeared to be related to preterm delivery rather than intrauterine growth restriction. Subsequently, at least one further study has been conducted with a sample of 922 African American, low-income pregnant women recruited in four hospital-based prenatal clinics in Baltimore, Maryland (Orr et al.,

2000). Women with unintended pregnancies were 1.82 times more likely to deliver their infants preterm, after adjustment for clinical and behavioral factors associated with preterm delivery.

Thus, although the research available on the association of the intendedness of pregnancy and preterm delivery is limited, that which is available suggests that women with unintended pregnancies are more likely to deliver preterm, and as a consequence, their infants are at higher risk of being of low birth weight. Understanding the pathways from unintended conception to preterm labor and delivery by the use of multilevel approaches would be useful in elucidating the etiology of preterm birth for at least some subgroups of women. Unmeasured socioeconomic factors that may be confounded with unintended pregnancies must be carefully controlled in future studies. In addition, it is critical to refine measures of intendedness to be sure they are valid and reliable if this arena of research is to be pursued. Reducing unintended pregnancies through family planning and other mechanisms could indirectly reduce the rates of preterm delivery and related adversities (IOM, 1995). Disparities in pregnancy outcomes, including preterm birth, could also be reduced by paying attention to the intendedness of a pregnancy (Hogue and Vasquez, 2002).

SUMMARY AND FUTURE DIRECTIONS FOR RESEARCH

Among the behavioral and psychosocial factors considered, the one that shows the most consistent evidence of having an adverse impact on the risk of preterm birth is cocaine use. Dietary constituents have been examined to a limited degree, with mixed evidence on the potential benefits of increased levels of iron, long-chain fatty acids, folate, and vitamin C being found. Although none of these dietary constituents is well established as having effects that prevent preterm birth, all warrant further evaluation. Leisure time physical activity has been associated with a reduced risk of preterm birth, but the implications for causality are unclear. Employment alone is nonspecific as a factor related to preterm birth, and meaningful etiologic research of this association is likely not possible. Although vaginal douching is of interest as a cause of preterm birth, given the concern with reproductive tract infections and the different prevalences of such infections between African American and white women, evidence of an influence on preterm birth is lacking thus far.

The evidence is fairly consistent that the occurrence of large numbers of major life events and the experiencing of severe life events during pregnancy are associated with preterm birth. Studies of chronic and catastrophic stress exposures are fewer in number, but such exposures also appear to contribute to preterm delivery, although more research in this area is needed. Past research findings are also consistent in pointing to maternal anxiety, espe-

cially anxiety over the pregnancy itself, as a risk factor for preterm delivery. In contrast, recent prospective studies on depression do not suggest a strong pattern for depression as a risk factor for preterm delivery; rather, these studies indicate that prenatal maternal depression may predict birth weight and fetal growth. The emerging literature on racism and preterm delivery suggests that racism, a possible stressor throughout the lifetimes of African American women, contributes to the explanation for racial-ethnic disparities in the rates of both preterm birth and low birth weight.

The results of more than two decades of observational studies on naturally occurring social support do not confirm a hypothesized link between maternal social support and preterm delivery; however, the studies do provide fairly consistent evidence for a direct association between social support and infant birth weight. Similarly, the provision of additional support to pregnant women during controlled intervention studies has not reduced the likelihood that the mother will give birth too early, although it does appear to have other benefits for women's health care and psychosocial adjustment. The few available studies on maternal self-esteem, mastery, and optimism provide little evidence for associations with preterm birth specifically, although the concept of perceived control may be a risk factor. Finally, preliminary research on the association of the intendedness of the pregnancy and preterm delivery suggests that women with unintended pregnancies are more likely to deliver their infants preterm.

The foregoing reviews and discussion of behavioral and psychosocial factors involved in the etiology of preterm birth give rise to some suggested future directions for researchers:

- At present, many studies of birth outcomes do not use preterm birth as a study outcome. Instead low birth weight is often used as a proxy. As stated earlier in this report (see Chapter 2), low birth weight can be caused by both preterm birth and fetal growth restriction, two conditions with some overlapping but also divergent determinants and pathways. Future research needs to define preterm birth and small for gestational age as specific and distinct study outcomes and should not use low birth weight as a proxy for preterm birth. In addition, attention should be paid to whether the onset of labor is spontaneous.
- Studies of behavioral risk factors and preterm birth should examine constellations of lifestyle factors rather than individual behaviors in isolation to elucidate possible etiologic pathways for specific subtypes of preterm delivery.
- Studies of stress and preterm birth should focus on specific components or factors, such as anxiety and hypothesized pathways from this condition to preterm birth. There is a pressing need for more theoretical analyses on the intensity and duration of distinguishable emotional states and

their consequences for pregnancy outcomes, such as spontaneous preterm labor, spontaneous rupture of membranes, and fetal growth restriction.

- Future studies on the association between stress and preterm birth should consider the unique forms of stress that specific racial and ethnic groups experience by using culturally valid measures in efforts to determine the optimal risk factors for specific subgroups of the population.
- Studies on the association between racism and preterm birth warrant follow-up for replication and further clarification to understand the specific exposures and mechanisms that pose a risk.
- Understudied topics that may be promising avenues for future research are the characteristics of daily activity and employment, as well as activity in the home and work contexts, including physical strain, occupational stress, and the effects of domestic violence during pregnancy.
- Attention to the intendedness of pregnancy is warranted to determine whether it is a risk factor for preterm birth rather than other outcomes, such as intrauterine growth restriction, and the pathways to such outcomes.
- Further research on personal resources, such as self-esteem, mastery, and control, may be warranted if it is conducted with a strong theoretical basis on the pathways to preterm birth. More generally, there is a need for theoretical models of the pathways from the presence of psychosocial conditions, including stress, social support, and other resilience factors, to preterm birth as a basis for ongoing observational research. These models should address the interrelationships of psychosocial conditions with biological and behavioral conditions by use of a multilevel approach.
- A more integrative approach to understanding individual-level factors in prematurity is needed. This will require the use of both a longitudinal integration linking a woman's life history to her vulnerability to preterm delivery and a contextual integration linking a woman's individual biology, psychosocial processes, and behaviors to the multilevel, multiple determinants of preterm birth (Misra et al., 2003).