The most important nine months of our lives are probably the nine months we know the least about.

Distinguished professor, Christopher Coe, “hit the nail right on the head” with the words above, delivered in a plenary lecture at a 2008 scientific conference. We know relatively little about biopsychosocial processes in pregnancy, yet we are learning that this short period of the life span as a fetus has profound consequences for the rest of our lives. We focus here on only one aspect of this topic, the role of stress in pregnancy and its effects on preterm birth. As with the study of the prenatal period in general, the study of the effects of stress in pregnancy has changed dramatically in the past decade from a small amount of inconclusive research conducted mainly in medicine to a sizable body of multidisciplinary studies evolving at lightning speed. As a 1990 review pointed out (Lobel & Dunkel-Schetter, 1990), investigations until then had been largely retrospective with weak conceptualizations and measures of stress, and many other methodological problems limiting conclusions (cf. Paarlberg, Vingerhoets, Passchier, Dekker, & Can Geijn, 1995). In the intervening 20 years, research scientists from many disciplines have contributed to a significant body of stronger research demonstrating that stress in one form or another during pregnancy is associated with preterm birth, low birth weight, maternal postpartum depression, infant complications, and developmental effects lasting long after infancy and even into adulthood (Beydoun & Saftlas, 2008). Furthermore, research on mechanisms has suggested that stress operates through neuroendocrine, immune, and behavioral pathways during pregnancy to influence specific outcomes in complex ways (e.g., Coussons-Read, Okun, & Simms, 2003; Hobel, Goldstein, & Barrett, 2008).

Before we explore the state of knowledge on this issue in detail, we note that progress in the investigation of stress in pregnancy has been challenging. Although research scientists in diverse disciplines agree that they must collaborate to study complex biopsychosocial processes in pregnancy, their goals remain different as do their areas of expertise. Finding effective interventions and policies are pressing public health needs in the United States (IOM, 2006) dictating research approaches that differ from basic scientific discovery, yet both are needed. As with most multidisciplinary work, progress can be slow and the process is cumbersome. Halbreich (2005) stated, “Currently the multiple clinical and research disciplines that are concerned with the various aspects of pregnancy, delivery and postpartum period are not conceptually and practically integrated” (p. 1312). This remains the context within which this body of research is now growing.

THE DILEMMA OF DEFINING STRESS

There is no consensus on the definition of stress for studying its contribution to adverse outcomes of pregnancy. In fact, many pregnancy researchers have treated major life events as a proxy and de facto definition of stress. Others view stress as any physiological threat, including physical strain, exercise, fasting, or sleep deprivation. Still others conceptualize stress as appraisals of threat, consistent with the psychological literature (Cohen, Kessler, & Gordon, 1995; Lazarus & Folkman, 1984). In keeping with a lack of consensus on definitions, measures of stress vary considerably and are inconsistently evaluated for the quality of measurement. Relatively few researchers use a multidimensional approach to compare measures, despite evidence of the value of this approach in prenatal stress research (e.g., Dole et al., 2003; Lobel, Dunkel-Schetter, & Scrimshaw, 1992; Roesch, Dunkel-Schetter, Woo, & Hobel, 2004). In our work, we use the term stress as a rubric or umbrella concept, following the work of Richard Lazarus (Lazarus, 1966, 1968). The overarching concept may then be divided into stressors (environmental exposures) and

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1 The relevant experts are physicians from obstetrics and pediatrics, health and developmental psychologists, social scientists, endocrinologists and immunologists, community health researchers, and epidemiologists.
responses (including biological, emotional, cognitive, and behavioral reactions). A further theoretical component is cognitive appraisals of stress, which operate as a critical mediator between stressors and responses in human research (Lazarus & Folkman, 1984). It is not easy to study the unfolding of dynamic stress processes (stressors, appraisals, responses) in pregnancy because a multitude of stressors and responses unique to each woman occur over the course of 9 months. Therefore, researchers have had to conduct observational investigations in which stressors and responses are assessed using self-report and aggregated over specific time periods within the study. Measures of life events (stressors) and of anxious and depressed mood (i.e., presumed responses to stressful conditions) have been the most common. Only recently have experimental studies of stress reactivity in pregnant women begun to appear (e.g., Hatch et al., 2006), which add to the larger body of evidence from observational research.

Intervention research on pregnancy has generally not been designed to pinpoint the role of stress in reducing rates of preterm birth, although such approaches are very valuable (cf. Bastani, Hidarnia, Montgomery, Aguilar-Vafael, & Kazemnejad, 2006).

We have been working individually and together on stress in pregnancy for many years endeavoring to make inroads. We share a commitment to bringing strong psychological theory and methods to the endeavor. In our multiple collaborations with health and biological scientists, we have tackled the challenges inherent in this research. In this chapter, we limit our attention to the effects of stress on preterm labor and delivery. Related findings on low birth weight are sometimes noted, although that is not the main focus. Our goals here are to review current evidence on stress and preterm birth, discuss primary hypothesized and known mechanisms of these effects (HPA, immune, behavioral), describe models of stress and preterm birth, and note larger theories of stress as they might enrich this body of work. In closing, we highlight promising directions for further inquiry.

PREVALENCE AND CONSEQUENCES OF PRETERM BIRTH

Preterm birth is the birth of a baby by any means (vaginal or Caesarian section) before 37 weeks' gestation, whereas normal gestation is 40 weeks. Preterm birth (PTB) is a contributor to other adverse birth outcomes, particularly low birth weight (LBW; defined as 2,500 grams or less) and infant mortality. Rates of these three correlated outcomes (PTB, LBW, and infant mortality) are high in the United States, particularly compared to other developed countries (MacDorman & Mathews, 2008). The United States typically ranks 27th. However, there has been a decline in overall infant mortality rates in the United States over the past few decades, with a simultaneous increase in PTB and LBW (Alexander & Slay, 2002), due largely to advances in neonatal intensive care. From 1990 to 2004, the rates of preterm birth rose from 10.6% to 12.5% of live births in the United States, an increase of more than 15% (Alexander, 2006, see Appendix A in 2006 IOM report). In 2005, there were over 4 million births in the United States of which 12.7% were preterm (about 1 in 8 births) and 8.2% were LBW (MacDorman & Mathews, 2008).

Adding to the complexity of this issue is a striking ethnic disparity in both PTB and LBW, with African Americans at much higher risk. In 2005, the rate of preterm birth among Black women in the United States was 18.1% compared to rates of 10.5% for Asian and Pacific Islander women and 11.5% for White women. The Hispanic rate was 12% overall. These disparities are not fully explained by socioeconomic status, maternal risk behaviors, genetics, or prenatal care (Lu & Haltin, 2003). Reducing rates of PTB, LBW, and infant mortality, along with eliminating disparities in these rates, are top public health priorities in the United States and have been for some time. Healthy People 2010 (www.healthypeople.gov), a set of federal objectives for increasing the health of the population, included the goal of reducing total preterm births to no more than 7.6% of live births. Still, high PTB and LBW rates persist despite considerable effort directed at their reduction. Thus, further research on both etiology and prevention is essential.

High rates of PTB and related adverse outcomes are of public health concern because of their severe consequences. Besides risk of death (i.e., neonatal and infant mortality) for those born especially early and/or small, PTB poses significant risk of complications at birth, pediatric problems in infancy and childhood, developmental disorders, adult health risks, and lifelong disabilities. Preterm (PT) infants are often hospitalized in the intensive care unit (ICU) for several weeks and suffer higher rates of respiratory problems, infection, and feeding difficulties, together with disrupted parent–infant contact. When they go home, caring for preterm infants presents special challenges. For example, they may be frightening for parents to care for and difficult to comfort (Affleck, Tennen, & Rowe, 1991). Depending on how early the delivery is and the presence of any complications at birth, infants born preterm have more pediatric visits for illness, suffer higher rates of cognitive and learning difficulties, and show poorer growth and development. There are higher risks of short- and long-term pulmonary, ophthalmologic, and neurologic morbidity and delayed psychomotor development (Kramer, 2003). Higher economic costs to families and society are further consequences of PTB. An Institute of Medicine (IOM) report estimated the cost of PTB to be $26.2 billion in 2005, two thirds of which...

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2 One reason for increased rates of preterm birth is an increase in multiple gestation or multiple births (e.g., twins, triplets). However, this does not account entirely for the increase in preterm birth, which remains high in singleton births.
was for medical care (Zupancic, 2006, see Appendix D in 2006 IOM report).

**PATHOPHYSIOLOGY OF PRETERM LABOR AND DELIVERY**

It is important to distinguish the various proximal causes of preterm birth. First, spontaneous preterm labor is the natural onset of labor defined as premature contractions before 37 weeks’ gestation. When it cannot be arrested by intervention, early labor may result in a preterm birth before 37 weeks. Approximately half of all preterm births occur in this way. In another 30% of cases, labor is preceded by preterm premature rupture of the membranes (referred to as PPROM), which leads to the onset of early labor either spontaneously or by induction to protect the fetus. The causes of PPROM are overlapping with those of spontaneous preterm labor without early rupture of membranes, and both may involve a role for maternal stress. In contrast, medically induced preterm birth, also called “indicated delivery,” is physician-initiated delivery for the benefit of the fetus or the mother via Caesarian section or by induction of labor (estimated as 20% of PTB cases). With a few exceptions, maternal prenatal stress is not relevant to early delivery for this last group. Certain conditions of pregnancy such as pregnancy-induced hypertension and pre-eclampsia that are direct contributors to indicated preterm birth (Klonoff-Cohen, Cross, & Pieper, 1996; Landsbergis & Hatch, 1996) may involve maternal stress as a precursor. Our focus in this chapter and in most research presently is on spontaneous preterm birth with or without PPROM, rather than indicated preterm birth.

Until recently, the pathophysiology of early labor was believed to be a single process regardless of how and when early labor began (anywhere from 22 weeks to 37). However, it is now accepted that there are multiple physiological pathways to preterm labor distinguishable, in part by when in gestation labor begins. This can be characterized as multiple upstream processes leading to a single downstream pathway to labor. According to a panel of experts preterm birth has heterogeneous origins that result in common biological pathways and that lead to relatively few clinical presentations (IOM, 2006).

**INFLAMMATORY/IMMUNE PATHWAY**

Inflammation is a primary process through which tissues deal with both infectious and noninfectious insults. The inflammatory response consists of increases in blood flow, increases in permeability of blood vessels, and migration of fluids, proteins, and white blood cells to the site of an injury or infection. Inflammation is central to reproductive success, playing a role in implantation of the embryo, maintenance of pregnancy, and parturition (Romero, Gotsch, Pineles, & Kusanovic, 2007). However, an exaggerated inflammatory response is a recognized contributor both to preterm labor and PPROM (Goldenberg, Hauth, & Andrews, 2000). For example, proinflammatory cytokines are involved in the ripening of the cervix in term deliveries, but overproduction of these cytokines is associated with PTB (Keelan et al., 2003). Bacterial intrauterine infections are the leading cause of infection-related preterm birth. The most common microorganisms found in the amniotic cavity are genital *Mycoplasma* species, which reflects the finding that the most frequent pathway through which intrauterine infections occur is ascension from the vagina and cervix (Goldenberg, Culhane, Iams, & Romero, 2008). Other known sources of infection related to PTB include lower genital tract infections, systemic maternal infections (e.g., malaria, kidney infection), and periodontal disease (Romero et al., 2007; Xiong, Buekens, Fraser, Beck, & Offenbacher, 2005). (There is little evidence supporting a role of viral infections such as influenza in PTB [Goldenberg et al., 2008]).

Inflammation due to bacterial systemic or maternal genital tract infections is estimated to account for 25% to 40% of PTB cases (Goldenberg et al., 2000) and may be responsible for up to 50% of PTB before 28 weeks (IOM). It is now believed that infection results in spontaneous preterm labor through stimulation of prostaglandins (lipid compounds with a wide range of strong physiological functions, including promotion of uterine contractility and increased production of proinflammatory cytokines by the mother and/or fetus in response to microbial invasion (Romero et al., 2006).

**THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL PATHWAY**

A second, neuroendocrine pathway, involving the maternal hypothalamic-pituitary-adrenocortical (HPA) axis and its effects on the fetal-placental unit, has been labeled the “stress pathway” by some obstetric researchers. Corticotropin-releasing hormone (CRH) is a neuropeptide primarily of hypothalamic origin that plays a central role in the control of pituitary-adrenal function and regulation of the physiological response to stress exposure (Vale, Spiess, Rivier, & Rivier, 1981). CRH stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH), which, in turn, activates the production of cortisol, a major stress hormone, by the adrenal cortex. During pregnancy this stress-sensitive peptide is synthesized by the placenta and rises exponentially in the maternal circulation over the course of normal gestation (Petruglia, Florio, Nappi, & Genazzani, 1996). Placental CRH (pCRH) levels during pregnancy

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3 PROM is referred to, colloquially, as “her water breaking.” It is important to note that PPROM is not a redundant term. PROM (premature rupture of membranes) refers to rupture of membranes prior to initiation of labor. PPROM (preterm PROM) means that this occurs before 37 weeks’ gestation.
have repeatedly been linked to timing of onset of partu-
rition and may be involved in the causal pathway (Smith,
Mesiano, & McGrath, 2002). Premature elevations (per-
haps beginning as early as 16–18 weeks’ gestation) and
steeper trajectories in CRH are reliable predictors of
eventual preterm labor and delivery (Holzman, Jetton,
Siler-Khodr, Fisher, & Rip, 2001; McLean et al., 1995; Smith
et al., 2009; Wadhwa et al., 2004; Wadhwa, Porto, Garite,
Chicz-DeMet, & Sandman, 1998). Further, elevated CRH
in the presence of lower levels of CRH-binding protein
may be particularly likely to increase the risk of PTB,
presumably because of the increased availability of
biologically active CRH (Hobel, Arora, & Korst, 1999;
Petraglia et al., 1997). In vitro studies suggest that when
released into the maternal compartment, the myome-
trium is a primary target for pCRH and its actions there
could influence uterine contractility (Markovic et al.,
2007; Yang, You, Tang, Gao, & Ni, 2006; You, Yang, Tang,
Gao, & Ni, 2006). Placental CRH also is released into the
fetal circulation, where it likely stimulates the produc-
tion of dehydroepiandrosterone sulfate (DHEA-S), the
precursor for placental estriol synthesis, from the fetal
adrenals, providing an additional route through which
pCRH might affect uterine contractility (Smith, Mesiano,
Chan, Brown, & Jaffe, 1998). Given these associations,
it is probable that pCRH is a causal determinant in the
pathway leading to preterm birth. However, to date, its
precise role in this complex process has yet to be fully
elucidated. The activation of the maternal HPA axis due
to stress exposure early in pregnancy, with consequences
for the fetal HPA axis and the placenta, is believed to be a
primary stress pathway to PTB.

TWO ADDITIONAL PATHWAYS

A third pathway that may also be sensitive to stress involves
abnormalities in placental vascular development that are
commonly observed in women who exhibit spontaneous
PTB and also PPROM. Vascular lesions of the placenta have
been detected in 34% of women with preterm birth and 35%
of women with PPROM, compared to 12% in women with
uncomplicated term deliveries (Arias, Rodriguez, Rayne, &
Kraus, 1993). Placental lesions can include those resulting
from improper early placental development (specifically,
failure of trophoblast invasion and physiological transforma-
tion of the spiral arteries), acute atherosclerosis, maternal or
fetal thrombosis (Khong, 2004). Vascular lesions may lead
to PTB by causing placental ischemia or alterations in the
microcirculation of the placenta. Plausible potential mecha-


membranes. There is little or no recognized contribu-
tion of stress in this multiple gestation pathway.

Before further exploring mechanisms further, we
examine the evidence for stress as a contributor to pre-
term birth.

EVIDENCE FOR STRESS
CONTRIBUTING TO PTB

For decades, there have been studies published suggest-
ing that women who are under stress are at higher risk
of adverse birth outcomes (Dunkel-Schetter, Gurung,
Lobel, & Wadhwa, 2000). However, the evidence has
been only suggestive until recently because of impre-
cision and lack of replication. An earlier careful review
by Savitz and Pastore (1999) of 20 of the more rigorous
studies concluded that it was difficult to draw conclu-
dions due to methodological limitations. Study designs
until that time had been a mix of retrospective and
case-control investigations, with relatively few utilizing
prospective studies. Approximately, half of the studies
reviewed found associations of stress and preterm birth
or length of gestation. One expert summed it up thus:
“Maternal psychosocial processes in pregnancy are at
least as important and warrant the same degree of fur-
ther consideration and study as other established obstet-
ric risk factors because the overall magnitude of their
independent effect size on prematurity-related outcomes is
comparable” (Wadhwa et al., 2002, p. 152).

In recent years, many more studies have been pub-
lished on this topic, often with prospective designs, large
sample sizes, and appropriate controls. Recent reviews
concur that the evidence regarding stress as a signifi-
cant independent risk factor for spontaneous preterm
Labor and delivery is now clearer (Beydoun & Saftlas,
2008; IOM, 2006). Beydoun and Saftlas (2008) report that 9 of
11 studies between 2000 and 2006 found significant effects
of prenatal maternal stress on length of gestation or risk of
preterm labor or birth, although not all studies adjusted
for appropriate control variables. They conclude that
evidence consistently suggests that exposure to stressful
stimuli increases the risk of preterm birth.

Another review was published in an Institute of
Medicine report on causes and consequences of PTB
(Savitz & Dunkel-Schetter, 2006). That review of about
two dozen studies is organized according to life events,
chronic and catastrophic stress exposures, emotional and
affective states (anxiety, depression), and other forms of
exposure (occupational stress and personal violence).
It concludes that the most consistent evidence is for anxiety
as a risk factor, particularly anxiety regarding pregnancy.
The present chapter’s review of the evidence is updated
to include many recent studies and is organized similarly
by stress concepts: episodic stressors, catastrophic/trau-
matic events, chronic stress, emotional states, and preg-
nancy anxiety/stress. Tables 24.1 through 24.4 categorize
<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stressor: Life events</strong> Barbosa (2000)</td>
<td>472 African American women</td>
<td>Prospective</td>
<td>Significant effect for loss events but not total life events</td>
</tr>
<tr>
<td>Dole et al. (2003)</td>
<td>1,962 North Carolina women</td>
<td>Prospective</td>
<td>Negative impact of life events predicted PTB (RR = 1.8)</td>
</tr>
<tr>
<td>Goldenberg et al. (1996)</td>
<td>1,491 pregnant women with previous PTB, 69% Black</td>
<td>Prospective</td>
<td>Nonsignificant association between LE and PTB</td>
</tr>
<tr>
<td>Hedgesaa, Henriksen, Secher, Hatch, and Sabroe (1996)</td>
<td>5,873 Danish women</td>
<td>Prospective</td>
<td>I or more stressful LE between 16 and 30 weeks gestation associated with PTB (OR = 1.76)</td>
</tr>
<tr>
<td>Lobel et al. (2000)</td>
<td>129 high-risk pregnant women</td>
<td>Prospective</td>
<td>Nonsignificant association between LE number and impact with GA</td>
</tr>
<tr>
<td>Kramer et al. (2009)</td>
<td>5,337 Canadian women</td>
<td>Prospective</td>
<td>Negative LE not associated with PTB</td>
</tr>
<tr>
<td>Lobel et al. (2008)</td>
<td>279 pregnant women</td>
<td>Prospective</td>
<td>Nonsignificant association for LE number and impact with GA</td>
</tr>
<tr>
<td>Lu &amp; Chen (2004)</td>
<td>33,542 PRAMS cohort</td>
<td>Retrospective</td>
<td>Nonsignificant association between LE and PTB</td>
</tr>
<tr>
<td>Messer et al. (2005)</td>
<td>1,908 pregnant women in NC</td>
<td>Prospective</td>
<td>Highest quartile of negative LE associated with PTB</td>
</tr>
<tr>
<td>Nordentoft et al. (1996)</td>
<td>2,432 Danish women</td>
<td>Prospective</td>
<td>Severe life events predicted PTB (OR = 1.14 controlling for covariates)</td>
</tr>
<tr>
<td>Parker-Dominguez et al. (2005)</td>
<td>178 African American women assessed at three times in pregnancy starting at 18–20 weeks</td>
<td>Prospective</td>
<td>Number of LE predicted GA</td>
</tr>
<tr>
<td>St. Laurent et al. (2008)</td>
<td>1,602 Montreal</td>
<td>Prospective</td>
<td>11-item measure in French indirectly predicted GA in path model via smoking</td>
</tr>
<tr>
<td>Zambrana et al. (1999)</td>
<td>1,071 low-income Mexican immigrant, Mexican American, &amp; Black pregnant women</td>
<td>Prospective</td>
<td>Number and impact of LE predicted GA as part of latent factor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample</th>
<th>IV</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stressor: Catastrophic/tranamatic events</strong> Berkowitz et al. (2003); see also Engel et al. (2005)</td>
<td>187 pregnant women exposed to disaster and 2,367 control women not exposed in pregnancy</td>
<td>Exposure to World Trade Center disaster in NYC</td>
<td>Nonsignificant differences in GA and PTB between groups</td>
</tr>
<tr>
<td>Eskenazi et al. (2007)</td>
<td>1,660,401 NY state birth records from 1996 to 2002</td>
<td>Present on Sept 11th terrorist attacks in NYC or upstate NY</td>
<td>Increase in delivery of infants weighing &lt;2,000 g in week after Sept 11 and no effect in comparison area</td>
</tr>
<tr>
<td>Glynn et al. (2001)</td>
<td>40 women experiencing Northridge, CA earthquake</td>
<td>Time in gestation or postpartum when earthquake occurred</td>
<td>Shortest gestation among women experiencing earthquake in first trimester</td>
</tr>
<tr>
<td>Hultink et al. (2008)</td>
<td>121 adolescent Finnish twins exposed in utero; 157 unexposed controls</td>
<td>Chernobyl nuclear disaster exposure during second trimester</td>
<td>Longer GA among exposed twins</td>
</tr>
<tr>
<td>Kuvacic et al. (1996)</td>
<td>Croatian pregnant women grouped as free (712) or expatriated (593 refugees)</td>
<td>Free or experienced stress due to expatriation during occupation in Croatia</td>
<td>Expatriated women delivered PT twice as often as those free</td>
</tr>
<tr>
<td>Lederman et al. (2004)</td>
<td>300 women in NYC during World Trade Center attack</td>
<td>Trimester when occurred and distance from WTC</td>
<td>Women in first trimester had shorter GA</td>
</tr>
<tr>
<td>Levi et al. (1989)</td>
<td>86 pregnant women exposed to Chernobyl nuclear disaster in Sweden early in gestation</td>
<td>Retrospective</td>
<td>Shorter GA (not PTB) associated with anxiety</td>
</tr>
<tr>
<td>Noll et al. (2007)</td>
<td>Case/control study: 68 child sexual abuse, 56 without</td>
<td>History of child sexual abuse</td>
<td>Higher risk of PTB in those with history of childhood sexual abuse</td>
</tr>
<tr>
<td>Rich-Edwards et al. (2005)</td>
<td>606 Boston women pregnant during the Sept 11th terrorist attacks</td>
<td>Comparison to women who delivered before Sept 11</td>
<td>Longer GA and lower risk of PTB among those in first trimester in Boston during Sept 11 attacks</td>
</tr>
<tr>
<td>Xiong et al. (2008)</td>
<td>Hurricane Katrina</td>
<td>High versus low exposure to the hurricane during pregnancy or immediately before conception</td>
<td>Increased risk of PTB</td>
</tr>
</tbody>
</table>

GA, gestational age at birth; LE, life events; OR, odds ratio; PRAMS, a specific pregnancy cohort study; PTB, preterm birth (<37 weeks); RR, relative risk.
the studies accordingly. When multiple measures of stress could be evaluated individually, a study may appear in more than one table.

Table 24.1 includes studies on episodic forms of stress. The largest numbers of studies have examined life events or major episodes that happen to individuals. In total, 8 of the 14 studies on life events showed significant effects in the expected direction. Of the 8, 6 involved very large sample sizes. Considered together, these studies suggest that exposure to certain types of life events (loss events, more severe events) and to very high numbers of life events increase risk of PTB. An additional study in a large Canadian sample showed indirect effects of life events on gestational age that were mediated by cigarette smoking (St. Laurent et al., 2008).

A second form of episodic stress shown in Table 24.1 is catastrophic events, referring to large-scale, destructive occurrences that fall outside the normal range of life experiences. Five of the nine studies on exposure in pregnancy document adverse effects of catastrophic events on gestational age (GA) or PTB. Several of these focused on the effects of the terrorist attacks in the United States on Sept 11th; most demonstrated significantly shorter gestational length among women exposed to the attack (e.g., Lederman et al., 2004), but in one study exposure to the terrorist attacks was associated counterintuitively with longer gestation (Rich-Edwards & Grizzard, 2005). Similar yet contrasting findings were obtained in two studies on the Chernobyl nuclear disaster; in one study, women who were exposed experienced shorter gestations (Levi, Lundberg, Hanson, & Frankenheuwer, 1989), but in a second study of twins exposed in utero compared to twins not exposed, longer gestation occurred among those exposed (Huizingk et al., 2008). Untangling stress-related physiological effects of the catastrophe from other possible effects, such as positive changes in behavior, increased support, and improved medical care, is necessary and may explain these contradictory results. More than half of the studies on catastrophes, however, are fairly consistent in demonstrating adverse effects on GA or PTB.

A final form of episodic stress is daily hassles. None of the four studies we located on this form of stress (not shown in table) had significant associations with GA or PTB (Jesse, Seaver, & Wallace, 2003; MacKey, Williams, & Tiller 2000; Paariberg, Vingerhoets, Heinen, Dekker, & & Can Geijn, 1996; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993).

Table 24.2 lists studies of various chronic forms of stress, including chronic strain, perceived stress, perceived racism, and neighborhood or community stressors. All five of the studies on chronic strain, measured either in general or in specific forms such as homelessness severity or household strain, show effects on PTB. These are mostly retrospective or case-control studies, but some involve controlled, prospective analyses in larger samples of high-risk women (e.g., Misra, O'Campo, & Strobino, 2001).

In contrast to these studies on chronic strain, only 4 of the 12 studies that measured appraised or perceived stress (see Table 24.2) showed effects on PTB. All of these studies used the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), which is not stressor specific and captures perceived strain and inability to control stress or cope. The largest study, conducted in the Netherlands, found PSS was associated with babies who were small for gestational age but not with PTB (Krabbendam et al., 2005). Three others with large samples, however, do report significant associations of PSS and PTB (Kramer et al., 2009; Messer, Dole, Kaufman, & Savitz, 2005; Zambrana, Dunkel-Schetter, Collins, & Scrimshaw, 1999). Thus, the utility of the PSS measure of perceived stress in predicting PTB remains unclear. In addition, two studies found that changes in PSS—both not levels at single time points—predicted PTB (Glynn, Dunkel-Schetter, Hobel, & Sandman, 2008; Ruiz, Fullerton, Brown, & Schoolfield, 2001).

Perceived racism, another chronic form of stress shown in Table 24.2, has been hypothesized to contribute to disparities in PTB and low birth weight. Yet only one of the three studies measuring racism that we located suggests effects on preterm birth. Nonetheless, an interesting study of California births before and after the 9/11 terrorist attacks, showed that the rates of preterm, LBW births were significantly higher after the attacks in women with Arabic surnames. Many additional studies (not listed in the table) have reported effects of perceived racism on birth weight (see review by Giscombe & Lobel, 2005). More rigorous research in this area is needed to draw conclusions about the effects of racism in African American and other minority groups on PTB as compared to effects on fetal growth or LBW.

Neighborhood- or community-level stress has been highlighted as an important group variable that may affect birth outcomes independent of individual-level factors and may account for race and social-class disparities (Culhane & Elo, 2005; IOM, Chapter 6, 2006). As shown in Table 24.2, seven of the eight studies on neighborhood stress factors show significant results on GA or PTB. For example, at the aggregate level, poverty, crime, and the racial composition of a community were all significant predictors of PTB in communities. The mechanisms through which neighborhood structural factors are associated with PTB and related outcomes presumably involve individual-level experiences of stress and adaptation (Moreno, 2003). More research on this pathway is needed.

Occupational stress is another form of chronic stress, but a review of the many studies on this topic is beyond the scope of this chapter and can be found elsewhere (Moorekewich, Luke, & Avni, 2000; Saurel-Cubizolles & Kaminski, 1986; Woo, 1997). There appear to be no risks associated with employment per se, but various characteristics of employment or housework are critical to understanding the effects of chronic strain in pregnancy. For example, both physical strain and psychological stressors, such as lack of control and work overload, have
Table 24.2 Chronic Forms of Stress

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic strain</td>
<td>496 women incarcerated during pregnancy</td>
<td>Case control</td>
<td>Risk of PTB increased compared to matched controls in women 30 years or older; but not among younger women</td>
</tr>
<tr>
<td>Hollander (2005)</td>
<td>739 low-income African American women</td>
<td>Retrospective</td>
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</tr>
<tr>
<td>Misra et al. (2001)</td>
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<td>Prospective at 20 and 30 weeks gestation</td>
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<td>Pritchard and Teo (1994)</td>
<td>237 Homeless women</td>
<td>Retrospective</td>
<td>Severity of homelessness (percent of life homeless) predicted PTB controlling for substance use, trauma, distress, race and ethnicity, income, medical risk</td>
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<td>GA</td>
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<tr>
<td>Gynne et al. (2008)</td>
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<td>Krabben et al. (2005)</td>
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<td>129 high-risk pregnancies</td>
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<td>Lobel et al. (2000)</td>
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<td>Messer et al. (2005)</td>
<td>178 African American women assessed at three times in pregnancy starting at 18–20 weeks</td>
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<td>PSS not associated with GA</td>
</tr>
<tr>
<td>Parker-Dominguez et al. (2005)</td>
<td>865 Brazilian pregnant women assessed &lt; 16 weeks, 20–26, 30–26.</td>
<td>PTB</td>
<td>No association with PTB</td>
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<td>Rondo et al. (2003)</td>
<td>78 pregnant low-income women assessed 23–26 and 31–35 weeks</td>
<td>GA</td>
<td>PSS levels not associated with preterm labor/birth (changes in PSS were significant)</td>
</tr>
<tr>
<td>Ruiz et al. (2001)</td>
<td>N = 106 pregnant women at 22–25 weeks</td>
<td>GA, BW</td>
<td>PSS associated with CRH but not GA</td>
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<tr>
<td>Ruiz et al. (2006)</td>
<td></td>
<td>GA</td>
<td>PSS associated with GA</td>
</tr>
<tr>
<td>Zambrana et al. (1999)</td>
<td>1,071 low-income Mexican immigrant, Mexican American and Black pregnant women</td>
<td>GA</td>
<td>PSS associated with GA</td>
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<tr>
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<tr>
<td>Perceived Racism</td>
<td>1,962 North Carolina women CA births 2000–2002 compared pre and post 9/11 terrorist attacks; racism imputed by name</td>
<td>PTB</td>
<td>Not associated with PTB</td>
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<tr>
<td>Dole et al. (2003)</td>
<td>CA births 2000–2002 compared pre and post 9/11 terrorist attacks; racism imputed by name</td>
<td>PTB</td>
<td>RRs of preterm LBW were higher pre/post 9/11 for Arabic-named compared to non-Hispanic White women</td>
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<tr>
<td>Lauderdale (2006)</td>
<td>124 African American and White women</td>
<td>GA</td>
<td>Associated with LBW adjusted for GA, but not with GA</td>
</tr>
<tr>
<td>Parker-Dominguez et al. (2008)</td>
<td>24 African American and White women</td>
<td>GA</td>
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<tr>
<th>Studies</th>
<th>Sample</th>
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<td><strong>Neighborhood/Community</strong></td>
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<td>Ahern et al. (2003)</td>
<td>417 African American births</td>
<td>Adverse neighborhood conditions predicted PTB with controls in model</td>
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<tr>
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<td>1,244 White births</td>
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<tr>
<td>Bell et al. (2006)</td>
<td>2002 African American births in major metropolitan areas (434,376) linked to census tract data</td>
<td>Greater isolation from other African Americans and lower clustering of African Americans associated with PTB and other adverse outcomes</td>
</tr>
<tr>
<td>Dole et al. (2003)</td>
<td>1,962 North Carolina women</td>
<td>No association with PTB</td>
</tr>
<tr>
<td>Masi et al. (2007)</td>
<td>1991 birth data in Chicago linked to neighborhood characteristics (55,130 live births)</td>
<td>PTB higher in Whites and Hispanics living in census tracts with higher proportion of Blacks vs. same race tracts (group density)</td>
</tr>
<tr>
<td>Messer et al. (2006)</td>
<td>Wake County, NC geocoded for birth and crime records (13,960 births)</td>
<td>Neighborhood crime and deprivation associated with PTB for White and Black non-Hispanic women</td>
</tr>
<tr>
<td>Pickett et al. (2002)</td>
<td>417 African American and 1,244 White women delivering in San Francisco 1980–1990</td>
<td>Neighborhood SES factors and changes in neighborhoods over time were related to PTB in exploratory analysis</td>
</tr>
<tr>
<td>Pickett et al. (2005)</td>
<td>1,991 births in Chicago to African American mothers (25,286)</td>
<td>PTB effects of SES at group level and racial composition of tracts (qualified by interactions)</td>
</tr>
<tr>
<td>Reagan and Salsberry (2005)</td>
<td>1,033 Blacks; 1,664 Whites; 602 Hispanics</td>
<td>Neighborhood poverty rates and housing vacancy rates positively associated with rate of very PTB and inversely associated with rate of moderate PTB for Blacks only!</td>
</tr>
</tbody>
</table>

BW, birth weight; CRH, corticotropin-releasing hormone; GA, gestational age at birth; LBW, low birth weight; PSS, perceived stress scale; PTB, preterm birth (<37 weeks); RR, relative risk.

been examined. A large study of 16 European countries (Saurel-Cubizolles et al., 2004) found that women working more than 42 hours per week, standing more than 6 hours per day, and with low levels of job satisfaction were at greater risk of PTB (cf. Escrib-Arguir, Perez Hoyos, & Saurel-Cubizolles, 2001).

Table 24.3 lists studies on emotional states, including separate lists for anxiety, depression, and general distress. A total of 6 of the 11 studies on general or state anxiety show some impact on preterm birth or gestational age, although in all cases the effects are somehow qualified. For example, one reports effects for White women but not for Black women (Goldenberg, Cliver, & Mulvhill, 1996). Another showed effects in Hispanic and White women when state anxiety was combined with a measure of pregnancy anxiety (Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). Lobel et al. (2008) found significant correlations at two of three time points in mid-to-late pregnancy. A large Swedish study examined clinical diagnoses of anxiety disorders but found no significant link to PTB (Andersson, Sundstrom-Poromaa, Wulff, Astron, & Bixo, 2003). A sixth study found that trait anxiety was associated with spontaneous preterm labor in women with a history of PTB (Dayan et al., 2002).

Only 3 of the 14 studies in Table 24.3 that tested depressed mood or symptoms of trauma show effects on GA or PTB. Depressed mood or depressive symptoms were typically measured using the Center for Epidemiological Studies Depression scale. Two studies involved clinical diagnoses of depressive disorders, but neither found significant associations with PTB or GA (Andersson et al., 2003; Suri et al., 2007). Only one of the three studies showing effects of depressed mood had a large sample size (Ort, James, & Blackmore Prince, 2002), whereas 6 of the 11 studies with no effects had large samples. Compared to these relatively modest results supporting a link between depression and PTB, many more studies show effects of depressed mood on fetal growth or low birth weight (e.g., Diego et al., 2006).

Three studies (shown in Depression section of Table 24.3) tested the effects on PTB of posttraumatic stress disorder symptoms (PTSD), often associated with depression. These show equivocal results. One found no association of PTSD symptoms to PTB or GA in 187 women who were near the World Trade Center when it was attacked (Berkowitz et al., 2003). A second study found that a measure combining PTSD and depression was associated with significantly longer GA among a small sample of 52 pregnant women who were near the World Trade Center (Engel, Berkowitz, Wolff, & Yehuda, 2005). A third study found a marginally significant effect of symptoms of nonspecific trauma on PTB in a sample of 1,100 pregnant women but no effect of depressed mood (Rogal et al., 2007).
<table>
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<th>Study</th>
<th>Sample</th>
<th>IV</th>
<th>Results</th>
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<tbody>
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<td>Anxiety (general)</td>
<td>Andersson et al. (2003) 1,465 women in Sweden in two clinics</td>
<td>Clinical diagnostic assessment in second trimester</td>
<td>No differences in PTB between women with anxiety disorders in pregnancy and those without</td>
</tr>
<tr>
<td></td>
<td>Copper et al. (1990) 2,593 (63% Black; 35% White)</td>
<td>2 items on feeling nervous, tense and strained at 26 weeks gestation</td>
<td>Predicted PTB with controls for race, age, marital status, insurance, education, substances</td>
</tr>
<tr>
<td></td>
<td>Dayan et al. (2002) 634 French women</td>
<td>Trait anxiety at 20–28 weeks gestation</td>
<td>Associated with spontaneous preterm labor in those with a history of PTB</td>
</tr>
<tr>
<td></td>
<td>Glynn et al. (2008) 415 Pregnant women</td>
<td>State anxiety assessed at 19 and 31 weeks</td>
<td>Change in anxiety, but not level, predicted PTB</td>
</tr>
<tr>
<td></td>
<td>Goldenberg et al. (1996) 1,491 pregnant women who had previously given birth; 69% African American</td>
<td>Trait Anxiety (retrospective)</td>
<td>Significantly associated with PTB in White women, not in AA women</td>
</tr>
<tr>
<td></td>
<td>Lobel et al. (1992) 130 pregnant women</td>
<td>State anxiety over pregnancy</td>
<td>Associated with GA as part of latent factor</td>
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<tr>
<td></td>
<td>Lobel et al. (2000) 129 high-risk pregnant women</td>
<td>State anxiety combined three assessments mid to late gestation</td>
<td>Not associated with GA</td>
</tr>
<tr>
<td></td>
<td>Lobel et al. (2008) 229 pregnant women</td>
<td>State anxiety mid to late gestation</td>
<td>Associations with GA at 2 of 3 time points in mid to late pregnancy</td>
</tr>
<tr>
<td></td>
<td>Parker-Dominguez et al. (2005) 178 African American women</td>
<td>State anxiety assessed at three times in pregnancy starting with 18–20 weeks</td>
<td>Not associated with GA</td>
</tr>
<tr>
<td></td>
<td>Parkin et al. (1993) 1,515 White pregnant women in London</td>
<td>GHQ anxiety subscale assessed at 3 time points (17–36 weeks)</td>
<td>No association with PTB</td>
</tr>
<tr>
<td></td>
<td>Rinli et al. (1999) 230 Hispanic and White</td>
<td>State anxiety assessed at 28–30 weeks</td>
<td>Associated with PTB in combination with pregnancy anxiety (OR = 1.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>Andersson et al. (2003) 1,465 women in Sweden in two clinics</td>
<td>Clinical diagnostic assessment in second trimester</td>
<td>No association between depressive disorders in pregnancy and PTB</td>
</tr>
<tr>
<td></td>
<td>Berkowitz et al. (2003) 187 women near World Trade Center; 2,367 controls</td>
<td>PTSD</td>
<td>No association with PTB or GA</td>
</tr>
<tr>
<td></td>
<td>Copper et al. (1990) 2,593 (63% Black; 35% White)</td>
<td>Depression symptoms</td>
<td>No association with PTB</td>
</tr>
<tr>
<td></td>
<td>Dayan et al. (2002) 634 French women</td>
<td>EPDS at 20–28 weeks</td>
<td>Associated with spontaneous preterm labor in women who were underweight before pregnancy (BMI &lt;19)</td>
</tr>
<tr>
<td></td>
<td>Dole et al. (2003) 1,962 pregnant women</td>
<td>CESD</td>
<td>No association with PTB</td>
</tr>
<tr>
<td></td>
<td>Engel, Berkowitz et al. (2005)</td>
<td>PTSD/Depression</td>
<td>PTSD associated with longer GA and smaller head circumference</td>
</tr>
<tr>
<td></td>
<td>Goldberg et al. (1996) 1,491 pregnant women who had previously given birth; 69% Black</td>
<td>CESD</td>
<td>No association with PTB</td>
</tr>
<tr>
<td></td>
<td>Jesse et al. (2003) 120 rural pregnant women</td>
<td>Two depression screening items at 16–28 weeks</td>
<td>Associated with PTB</td>
</tr>
<tr>
<td></td>
<td>Kramer et al. (2009) 5,337 Canadian women</td>
<td>CESD score over 16</td>
<td>Not associated with PTB</td>
</tr>
<tr>
<td></td>
<td>Messer et al. (2005) 1,908 women at 24–29 weeks' gestation (PIN study in N. Carolina)</td>
<td>CESD</td>
<td>Not associated with PTB</td>
</tr>
<tr>
<td></td>
<td>Orr et al. (2002) 1,399 low-income African American pregnant women</td>
<td>CESD</td>
<td>Women in top 10% at greater risk of spontaneous PTB (adj OR = 1.96)</td>
</tr>
<tr>
<td></td>
<td>Parkin et al. (1993) 1,515 White pregnant women in London</td>
<td>GHQ depression subscale assessed at 3 time points (17–36 weeks)</td>
<td>No association with PTB</td>
</tr>
<tr>
<td></td>
<td>Rogal et al. (2007) 1,100 pregnant women</td>
<td>Depression/PTSD</td>
<td>Higher rate PTB for PTSD (p &lt; .055)</td>
</tr>
<tr>
<td></td>
<td>Suri et al. (2007) 90 women assessed prospectively (49 under treatment for MDD; 22 MDD without treatment; 19 comparisons)</td>
<td>SCID, Beck, Hamilton</td>
<td>No association with GA</td>
</tr>
<tr>
<td>Other emotions/general distress</td>
<td>Hedegaard et al. (1993) 5,872 Danish women</td>
<td>GHQ at 16 and 30 weeks gestation</td>
<td>Distress at 30 weeks associated with PTB</td>
</tr>
<tr>
<td></td>
<td>MacKey et al. (2000) 35 pregnant women hospitalized for preterm labor; 35 controls</td>
<td>POMS</td>
<td>Tension/anxiety and depression subscales associated with preterm labor</td>
</tr>
<tr>
<td></td>
<td>Neggers et al. (2006) 3,149 low-income predominately African American pregnant women</td>
<td>28 item psychosocial risk scale including negative affect, worry, and stress</td>
<td>Negative affect associated with PTB</td>
</tr>
<tr>
<td></td>
<td>Peacock et al. (1995) 1,513 White women assessed 17–36 weeks at three times</td>
<td>GHQ and 2 items on &quot;trouble with nerves and depression&quot;</td>
<td>No association with PTB</td>
</tr>
</tbody>
</table>

CESD, Center for Epidemiological Studies Depression scale; EPDS, Edinburgh Postpartum Depression Scale; GA, gestational age at birth; GHQ, General Health Questionnaire; OR, odds ratio; POMS, Profile of Mood States; PTB, preterm birth (<37 weeks); PTSD, posttraumatic stress disorder; SCID, Schedule of Clinical Indicators of Depression.
Studies on general distress use measures that combine symptoms of depression, anxiety, and other forms of psychopathology. Of the five studies on general distress shown in Table 24.3, four found adverse effects on PTB. The most recent is a study of 3,149 low-income and predominantly African American pregnant women in which negative affect was associated with PTB (Neggers, Goldenberg, Cliver, & Hauth, 2006). The largest, a 1993 study in Denmark, utilized a common general distress measure, the General Health Questionnaire (GHQ), which at 30 weeks predicted PTB but not at 16 weeks.

Table 24.4 contains all of the published studies we could locate on pregnancy anxiety and pregnancy stress. Notably, all but 1 is prospective, and 10 of 11 show effects on PTB. The 3 with the largest samples all confirmed the role of pregnancy anxiety in PTB (Dole et al., 2003; Kramer et al., 2009; Orr, Reiter, Blazer, & James, 2007). Thus, of all the emotional states covered in Table 24.4, pregnancy anxiety emerged as the strongest predictor.

There are a few studies in the literature that used combined measures of stress to test effects on preterm birth. Overall, they are mixed in their findings. About half show effects of unique composite indices on gestational age or preterm birth (Lobel et al., 1999; Zambrana, Scrimshaw, Collins, & Dunkel-Schetter, 1997) and the other half do not (Diego et al., 2006; Hobel, Dunkel-Schetter, Reoch, Castro, & Arora, 1999; Lobel, DeVincent, Kaminer, & Meyer, 2000; Lobel et al., 2008). For example, 130 pregnant women were followed throughout pregnancy with multiple measures of stress (perceived stress, state anxiety, distress from life events) that were later aggregated into a composite index summed over second and third trimester assessments (Lobel et al., 1992). This stress composite predicted earlier delivery as well as lower birth weight with medical risk factors controlled, including smoking. This finding was then replicated in a subsequent study in Los Angeles County with a much larger and more homogeneous sample of pregnant women of Mexican origin or descent and similar though slightly different stress measures (Zambrana et al., 1997).

In one further study of this type, three stress measures were compared in their predictive power; together, they predicted gestational age among a sample of 418 women delivering mostly at term; however, once again, the predictor that accounted for most of the effect was pregnancy anxiety (Roesch et al., 2004). As these studies illustrate, combining different stress measures has both advantages and disadvantages. If a set of stress measures are intercorrelated, their combined use as a measured variable or latent factor should increase the quality of the stress measure and the power to detect effects on the outcome. However, combining stress measures of different conceptional nature may not achieve this goal and can sacrifice the ability to determine which components have effects and which do not. Comparative analyses of different stress measures are valuable in pinpointing the relevant risk factors and in developing theories of mechanisms that are psychologically precise. Thus, we recommend the use of multiple stress measures in future research for the purpose of comparative analyses and, in some cases, for the formation of composite indices, but with a careful eye to how the individual components are interrelated, and with full reporting of their individual effects.

In addition to considering multiple measures of stress, it also is important to consider the pattern of stress, or stress profile, across gestation because there are predictable changes in stress responding as pregnancy progresses. On average, women show a decline in psychological and physiological stress responding during gestation (DiPietro, Costigan, & Gurewitsch, 2005; Glynn, Dunkel-Schetter, Wadhwa, & Sandman, 2004; Glynn, Wadhwa, Dunkel-Schetter, Chicz-DeMet, & Sandman, 2005).

<table>
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<tr>
<th>Study</th>
<th>Sample</th>
<th>Design</th>
<th>Results</th>
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<tbody>
<tr>
<td>Dole et al. (2003)</td>
<td>1,962 pregnant women</td>
<td>Prospective</td>
<td>Anxiety at 24–29 weeks predicted PTB (RR = 2.1) adjusted for alcohol and tobacco use</td>
</tr>
<tr>
<td>Kramer et al. (2009)</td>
<td>5,337 Canadian women</td>
<td>Prospective</td>
<td>Anxiety predicted PTB (OR = 1.5)</td>
</tr>
<tr>
<td>Lobel et al. (2000)</td>
<td>129 high-risk pregnant women</td>
<td>Prospective</td>
<td>Not associated with GA</td>
</tr>
<tr>
<td>Lobel et al. (2008)</td>
<td>279 pregnant women</td>
<td>Prospective</td>
<td>Pregnancy specific stress more strongly associated with GA than P5S or state anxiety</td>
</tr>
<tr>
<td>Mancuso et al. (2004)</td>
<td>282 diverse ethnicity</td>
<td>Prospective</td>
<td>Anxiety at 28–30 weeks (not at 18–24 weeks) predicted GA.</td>
</tr>
<tr>
<td>Miara et al. (2001)</td>
<td>739 low-income African American women</td>
<td>Retrospective</td>
<td>Pregnancy hassles not associated with PTB</td>
</tr>
<tr>
<td>Orr et al. (2007)</td>
<td>1,820 pregnant women (3/4 African American)</td>
<td>Prospective</td>
<td>Predicted risk of spontaneous preterm birth (OR = 2.7)</td>
</tr>
<tr>
<td>Parker-Dominguez et al. (2005)</td>
<td>178 African American pregnancies assessed at 3 times in pregnancy starting with 18–20 weeks</td>
<td>Prospective</td>
<td>Anxiety not associated with GA</td>
</tr>
<tr>
<td>Rini et al. (1999)</td>
<td>230 Hispanic and White at 28–30 weeks</td>
<td>Prospective</td>
<td>Combination of state and pregnancy-specific anxiety assessed for predicted GA.</td>
</tr>
<tr>
<td>Roesch et al. (2004)</td>
<td>418 African American, Latino and White pregnant women, mostly term deliveries</td>
<td>Prospective</td>
<td>Pregnancy specific stress predicted GA controlling for perceived stress and state anxiety</td>
</tr>
<tr>
<td>Wadhwa et al. (1993)</td>
<td>90 pregnant women</td>
<td>Prospective</td>
<td>Anxiety predicted GA and PTB</td>
</tr>
</tbody>
</table>

GA, gestational age at birth; OR, odds ratio; PTB, preterm birth (<37 weeks).
OTHER RISK FACTORS FOR PRETERM BIRTH

The role of stress as an independent risk factor for PTB must be tested with appropriate control of other known risk factors. Although there are many medical risk factors for PTB, the amount of variance they explain, either individually or in combination, is typically low. These include various medical history factors (LBW or PTB in a previous pregnancy; multiple second trimester spontaneous abortions [i.e., miscarriages]; prior first trimester induced abortion; history of infertility; nulliparity [i.e., no prior births]; cervical, uterine, and placental abnormalities; and DES exposure), and current pregnancy conditions (gestational bleeding, intrauterine growth retardation, preeclampsia, urogenital infections, inadequate weight gain). In addition, short stature and low prepregnancy weight or low body mass index are also risk factors (IOM, chapter 4, 2006).

Prenatal care has also been studied extensively, showing that late or no prenatal care generally increases risk of preterm birth, disproportionately so for Black and Hispanic women (Masi, Hawkley, Piotrowski, & Pickett, 2007) and high-risk pregnancies. Demographic factors associated with higher risk of PTB are single marital status, low SES (usually income/education), and age (under 17 years of age or over 40). SES is associated with PTB in studies abroad as well as in the United States. This link is attributed most often to associations of SES with work and physical activity, health behaviors (nutrition, smoking, substance use), medical conditions (gastrointestinal and sexually transmitted infections), prenatal care, and stress (see IOM, Chapter 6, for review). SES is predictive of PTB at both the individual and community level. That is, the socioeconomic characteristics of a woman (e.g., her education, occupational status, household income) and of her community (average household income in a neighborhood) both contribute to risk.

Proposed behavioral risk factors for PTB include tobacco use; use of cocaine, marijuana, and other illicit drugs; alcohol consumption; caffeine intake; dietary intake; sexual activity during late pregnancy; and physical activity. Many of these health behaviors have not proved to be as strongly associated with PTB as presupposed. For example, a “health practice” score combining alcohol, tobacco use, medical and dental care, vitamin use, and exercise was not associated with PTB in one large study (Neggers et al., 2006). The 2006 Institute of Medicine Review of the behavioral contributors to preterm birth concluded that “there is clear evidence that a favorable lifestyle and a greater degree of health consciousness are associated with reduced risk of preterm birth above and beyond what can be measured effectively and controlled in observational studies...continued efforts are needed to better understand and ultimately pinpoint the aspects of favorable lifestyle that are associated with a reduced risk of preterm birth” (IOM, 2006, p. 89).

Of these lifestyle factors, smoking is one of the more robust behavioral predictors of PTB and LBW (Ahern, Pickett, Selvin, & Abrams, 2003; Masi et al., 2007; McCormick et al., 1990; Paarlberg et al., 1999). A recent study in the Netherlands with a large sample found that smoking (especially late in pregnancy) was associated with LBW and PTB (Jaddoe et al., 2007). In addition, smoking contributes to PPROM.

Lobel, Hamilton, and Cannella (2008) provide a cogent review of the role of physical activity in the form of exercise and strenuous leisure activities. They argue that moderate physical activity is advantageous for pregnant women. Insufficient research is available to determine the effects of different levels or types of activity on PTB, although this remains an area of great interest. Another risk factor of growing emphasis is environmental exposure to toxic substances. Documented risk factors for preterm birth include exposure to lead, air pollutants, and tobacco smoke (Ritz, Yu, Chapa, & Fruin, 2000).

EVIDENCE FOR THE ROLE OF STRESS IN BEHAVIORAL PATHWAYS TO PRETERM BIRTH

There is considerable evidence that stress is associated with higher risk health-related behaviors in adults in general, and there is some evidence that stress is a contributor to poorer health behavior in pregnancy (Lobel et al., 2008). For example, Rodriguez, Bohllin, and Lindmark (2000) examined health behaviors in 350 nulliparous pregnant women and found that perceived stress at weeks 12 and 32 predicted smoking at weeks 20 and 32 of gestation.

St. Laurent et al. (2008) found that stress predicted gestational age at birth indirectly through its association with smoking. In a sample of 279 pregnant women,
Lobel et al. (2008) found that pregnancy-specific stress predicted health behaviors (cigarette smoking, caffeine consumption, unhealthy eating, vitamin use, and exercise) and also gestational age at delivery, but they found no evidence for a mediational pathway. There was, however, a mediated pathway from stress to birth weight; pregnancy-specific stress predicted birth weight through effects on smoking and preterm birth.

Hobel and Culhane (2003) reviewed evidence on maternal psychosocial stress, strenuous activity, and fasting as independent risk factors for PTB and LBW and noted plausible biological pathways. Another behavioral pathway, involves possible stress effects on low utilization of prenatal care. If women are overwhelmed by chronic strain and lack support, they may be unable to find time or transportation, manage the cost, or obtain low-cost services for prenatal care. In addition, highly stressed pregnant women may miss visits and show poor compliance with recommendations such as prenatal vitamins. Language problems and discrimination in health care settings can also pose barriers for minority and immigrant women. Understanding the multiple ways in which stressors pose barriers to prenatal care is an important understudied area.

EVIDENCE FOR THE ROLE OF STRESS IN IMMUNE, NEUROENDOCRINE, AND CARDIOVASCULAR PATHWAYS TO PRETERM BIRTH

Few studies have examined both exposures to psychosocial stress and potential neuroendocrine mediators in conjunction with birth outcomes. Despite this, there is some evidence to support the view that one avenue through which stress exposures result in preterm birth is through activation of the maternal HPA axis. First, during the prenatal period, exposures to or perceptions of psychosocial stressors, and also depression, have been linked to elevations in circulating stress hormones, including CRH, ACTH, and cortisol (Field et al., 2008; Mancuso, Dunkel-Schetter, Rini, Roesch, & Hobel, 2004; Rich-Edwards et al., 2008; Sarkar, Bergman, O’Connor, & Glover, 2008; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, & Sandman, 1996; Yim et al., 2009). Second, both in vitro and in vivo studies provide evidence that cortisol can stimulate the production of placental CRH (Petraglia, Sutton, & Vale, 1989; Sandman et al., 2006). Third, those studies that have utilized multiple prospective measures of both biological and psychological stress are consistent with the idea that the link between maternal psychosocial stress exposure and PTB may be mediated by alterations in HPA axis and placental function. For example, we have shown that elevations in stress and anxiety are associated with elevated CRH, which in turn predicts PTB (Hobel, Dunkel-Schetter et al., 1999; Mancuso et al., 2004). There are at least two other studies that have included measures of both psychosocial stress and HPA and placental hormones that have not replicated these associations (Erickson et al., 2001; Kramer et al., 2009). However, both of these studies measured psychosocial stress at only one prenatal time point, and this most likely poses a critical limitation on the ability to detect such associations.

Indirect evidence for a role of the immune pathway in the relation between stress and PTB is derived from our understanding of the relations between stress exposures and immune function in the nonpregnant state. It is well documented that both the sympathetic adrenomedullary (SAM) and HPA axes interact with the immune system and that chronic activations of these systems are associated both with inflammatory processes and immunosuppression (Malarkey & Mills, 2007). Further, exposures to stressors, in both humans and nonhuman animals, are associated with reduced natural killer cell and lymphocyte function, increased cytokine production, and increased susceptibility to, and duration of, illness (Cohen, Doyle, & Skoner, 1999; Glaser & Kiecolt-Glaser, 2005). Accumulating evidence also provides direct support for the hypothesis that the immune pathway mediates the relation between stress exposure and PTB. Among pregnant women, higher levels of chronic stress at both the individual and community levels (Culhane, Rauh, McCollum, Elo, & Hogan, 2002; Culhane et al., 2001), and also reports of higher levels of perceived stress over the previous month (Nelson et al., 2008), have been linked to the presence of bacterial vaginosis. In addition, high levels of prenatal stress are associated with elevated proinflammatory cytokines and C-reactive protein and also specifically influence lymphocyte production of proinflammatory cytokines (Coussons-Read, Okun, & Nettles, 2007; Coussons-Read, Okun, Schmitt, & Giese, 2005; Herrera, Alvarado, & Martinez, 1998). Both the findings linking stress exposures to susceptibility to infection during pregnancy, and the findings linking stress exposures to immune functions relevant to the physiological control of normal parturition and to PTB, provide support for the proposition that the adverse consequence of prenatal stress exposure on PTB operate, in part, through the immune/inflammatory pathway.

Although relatively few studies have examined the role of stress in the HPA and immune pathways to preterm birth, even less is known about the potential for stress to influence vascular processes associated with PTB. When vascular abnormalities of the placenta occur, they may be reflected in heightened resistance in the microcirculation of the placenta (Adamson, Morrow, Bascom, Mo, & Ritchie, 1989; Hossain & Paidas, 2007). Some studies have demonstrated an association between both biological and psychosocial indicators of stress and alterations in placental vascular resistance. Both CRH and cortisol levels have been linked to alterations in uterine and umbilical artery blood flow.
THEORY AND ANALYSIS OF STRESS AND PRETERM BIRTH MECHANISMS

THREE PART MECHANISTIC PATHWAY

The simplest schema for a theoretical approach to the study of stress processes in preterm birth is a three-part causal chain involving stressor–mediators–preterm birth. Table 24.5 indicates possible stressors, mediators, and outcomes in a model of spontaneous preterm birth.

As can be seen in the Table 24.5, there are many forms of stressors, many possible mechanisms, and one outcome, measured either continuously (GA, or gestational age, also called length of gestation) or as a dichotomy (PTB). A related trichotomy is term birth (>37 weeks), preterm birth (32–36 weeks), and very preterm birth (<32 weeks). Birth weight (BW) should always be studied in combination with PTB given the high degree of overlap as noted earlier. In the majority of studies of prenatal stress and preterm birth, the X variable (stress) is treated as unidimensional despite the range of different possibilities. In other words, the “upstream” factors in this schema (e.g., stressors) are usually treated somewhat simplistically, while the “downstream” factors (e.g., neuroendocrine and immune parameters) are much more differentiated.

Most studies examine only two of the three components in the chain, stress and outcome, stress and mediators, or mediators and outcome. Intensive, well-designed, prospective investigations evaluating the full mediated model are rare. As noted above, there is limited evidence for the three-part causal chain (mediational model), and some studies that have tested the

<table>
<thead>
<tr>
<th>X (Stressors)</th>
<th>Y (Hypothesized Mediators)</th>
<th>Z (Outcomes)</th>
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<tbody>
<tr>
<td>Episodic major events</td>
<td>Neuroendocrine</td>
<td>Gestational age (weeks)</td>
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<td>Chronic strain</td>
<td>Cortisol</td>
<td>Preterm birth (&lt;37 weeks)</td>
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<td>Trauma/loss</td>
<td>CRH</td>
<td>Birth weight (grams)</td>
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<td>Racism</td>
<td>ACTH</td>
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<td>Neighborhood stressors</td>
<td>Immune</td>
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<td>Emotional states</td>
<td>Proinflammatory cytokines</td>
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<td>Depressed mood</td>
<td>Immune suppression</td>
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<td>Anxiety (state or trait)</td>
<td>Cardiovascular</td>
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<td>General distress</td>
<td>Resting and ambulatory BP</td>
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<td>PTSD</td>
<td>Cardiovascular reactivity</td>
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<td>Pregnancy anxiety</td>
<td>Behavioral</td>
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<td>Pregnancy-specific stress</td>
<td>Physical activity/exercise</td>
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<td>Composite indices</td>
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<td>Substances (e.g., cocaine)</td>
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<td>Diet/nutrition</td>
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<td>levels over time (trajectories)</td>
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mediational model have not found significant effects. For example, our most recent work with a large cohort of women (N = 400 or more) tested four times prenatally beginning at 15-weeks gestation; we found no concurrent relations between measures of stress or negative affect and hormones of the HPA axis or placenta (cortisol, ACTH, CRH) at any time point. Thus, evidence for a simple neuroendocrine mechanism is not necessarily consistent (cf. Kramer et al., 2009).

We have pondered why there is not stronger evidence for the hypothesized mediation of the stress–preterm birth link. There are several possibilities. One observation is that research teams tend to be skilled in one piece of the pathway and not in others, so studies are imbalanced in this respect. Most studies are strong in either the study of psychosocial stress or the biological mediators, but not both. Some are weak in both areas but strong in their understanding of preterm birth and labor. Very few studies are strong in their approach to studying the health behavior mediators. Thus, unevenness in rigor of all components is a possible explanation for the lack of evidence for the mediational pathways. The solution is obviously to conduct better designed studies involving further collaboration among experts from the relevant disciplines. Another possible explanation is that the design and analytical strategies are not fully capturing the dynamic relations between physiological and psychosocial processes during pregnancy. To understand these complex relations, both longitudinal designs and analytic techniques such as multilevel modeling are needed in order to examine interrelationships over time.

IMPROVING THE STUDY OF STRESS AND PRETERM BIRTH

To improve existing research paradigms, perinatal researchers need to study stress more rigorously, relying more on theory and examining the multiple dimensions of stress. Measurement issues regarding reliability and validity must be addressed more adequately than in past. Many studies do not provide Cronbach’s alpha coefficients reflecting internal consistency estimates of the reliability of multi-item measures of stress, or the reliability estimates reported are marginal or too low to test hypotheses with adequate power. Stress instruments that are designed and validated in English must be translated into foreign languages with greater attention to whether the original concept is captured validly and reliably. Reliability of psychosocial instruments in different languages is often lower than in English, providing only weak tests. For example, research on Hispanic pregnancies is now being conducted in Spanish, but the quality of translations is frequently unknown or poor. Furthermore, some stress concepts do not generalize well across ethnic, cultural, and foreign populations (validity issues). These issues must be addressed thoughtfully to provide good tests of the stress–preterm birth hypotheses in the diverse populations that happen to be those of greatest risk and attention by policy makers. We have found this to be a rich area for basic researchers interested in culture as well (Campos et al., 2008).

If some dimensions of stress apply only to specific groups, it does not mean they are not valuable to study. Racism, for example, is a salient stressor for African Americans that may contribute to disparities in preterm birth. Similarly, anxiety in pregnancy has been shown to characterize Latina women in particular, especially new and unacculturated immigrants from countries with poor medical care (Rini et al., 1999; Scrimshaw, Zambrana, & Dunkel-Schetter, 1997). We must continue to develop population-specific concepts and measures of stress in order to improve our ability to test hypotheses well. In addition, we need stress concepts and measures that generalize well over ethnic, cultural, and international populations, with validation in different languages. The emergence of pregnancy-specific validated measures of stress and anxiety may help to abet this particular issue (cf. Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004; Lobel et al., 2008; Rini et al., 1999).

Insufficient sample sizes, heterogeneity within samples, and lack of control of confounding variables in tests of mediation also contribute to the weak evidence thus far. For instance, researchers must study either high-risk pregnancies or a mix of high and low risk because predominately low-risk populations usually have insufficient variability in stress or gestational age to test hypotheses well. Also, studies typically control for only some of the many risk factors (e.g., medical risk factors, health behaviors, demographics) or control for only a subset within a risk category (e.g., previous preterm birth but not other medical conditions, smoking but not other health behaviors, age but not education). This is often due to small sample size, but control for risk factors can be achieved by other means such as greater homogeneity in sampling. Sampling only one ethnic group or a group with common medical risk characteristics may require more time to recruit but may be a stronger research design, especially if the sample size is not in the thousands. These problems in study design and analyses render many previous tests of the mediational chain from stress to preterm birth underpowered to obtain significant results.

Researchers must also ask whether they are studying the HPA and immune systems in pregnancy carefully enough. Intensive, rigorous, prospective studies involving biological sampling with large samples are very rare (cf. Harville et al., 2008). Further, CRH, which has been such a promising marker in stress–PTB research, is very difficult and expensive to assay and is viewed as impractical for population studies in general (Latendresse, 2009; Latendresse & Ruiz, 2008). Furthermore, we should be examining diurnal cortisol rhythms (i.e., repeated assessments over the day), and cortisol response under challenge conditions (laboratory stress paradigm or waking responses), rather than taking a single snapshot of cortisol. In addition, behavioral health researchers who are expert in the study of
smoking, alcohol and drug use, nutritional analyses, and physical activity are needed to refine the measurement and analytical approaches to the study of these mediators (cf. Roelands, Jamison, Lyerly, & James, 2009; Zammit, Skouteris, Wertheim, Paxton, & Milgrom, 2008).

Regarding the outcome variables, the focus must zero in on spontaneous early labor, and theory must be applied to distinguish mechanisms involved in effects of stress on very early preterm birth versus later preterm birth. For example, if early birth results more often from immune dysregulation, one might examine pathways from prepregnancy and early pregnancy forms of stress hypothesized to influence specific immune factors.

Existing Models. For many years, there were no biopsychosocial conceptual models guiding work in this research area. Currently, there are several published papers specifying pathways to preterm birth, ranging from simple conceptual diagrams or schemes to complex frameworks. For example, Dr. Calvin Hobel, who published among the first mapping of hypothesized pathways from stress to preterm birth (Bragonier, Cushner, & Hobel, 1984), has detailed these pathways in a recent paper reflecting advances in our knowledge (Hobel, Goldsmith, & Barrett, 2008). Wadhwa et al. (2001) have spelled out the infection pathways in detail (see also Coussins-Read, Okun, & Simms, 2003). Wang et al. (2001) have laid out the pathogenic pathways to PTB focusing on gene–environment interactions and effects on mechanisms. In this excellent paper, social environmental risk and maternal and fetal genes interact to influence inflammation, HPA activity, utero-placental vasculopathy, and susceptibility to toxins, all leading to preterm labor, PPROM, induction, and ultimately, to PTB. Each of these models, however, focuses in detail on the biomedical side of the equation and is much sketchier on the psychosocial side.

Other models have developed the psychosocial pathways a bit further and incorporated sociodemographic factors usually with the goal of public health prevention. Hogue, Hoffman, and Hatch (2001) and Kramer, Goulet, Lydon, Seguin, and McNamara (2001), for example, both emphasized socioeconomic status and ethnic disparities in pathways from stress to PTB. Lu and Halfon (2003) applied a life-course perspective incorporating SES, behavior, prenatal care, stress, infection, race, and racism. Misra, Guyer, and Allston (2003) propose a multiple determinants model that also takes a life-span approach and incorporates preconception and interconception factors to improve perinatal health. This paper includes social, psychological, behavioral, environmental, and biological forces operating during pregnancy and influencing short- and long-term maternal and infant disease and complications, health and functioning, and well-being. Culhane and Elo’s (2005) conceptual framework includes neighborhood factors (social environment, service environment, physical characteristics) as well as individual-level factors (SES and demographic), which together lead to further individual-level factors (psychosocial and behavioral), stress physiology, and birth outcomes. Some approaches are even larger in scope, such as that of Halbreich (2005), which includes postpartum outcomes, offspring development, offspring long-term disorders, and next generation vulnerability in one comprehensive model.

In sum, there are now many models available to guide research. Nonetheless, we still need integration of these models into more comprehensive biopsychosocial frameworks with equal emphasis on biomedical, psychosocial, sociodemographic, and sociocultural factors. As with any good model, future frameworks must generate hypotheses that are testable. Since one comprehensive model may not be ideal, partial analyses are also valuable but, ideally, with further biopsychosocial linkages specified. In general, pregnancy research is not utilizing existing social and behavioral science theories or the newest empirical findings on stress and health (e.g., Gallo & Matthews, 2003; Hobfoll, Schwarzer, & Koo Chon, 1998). One prominent biopsychosocial theory regarding effects of stress on health via allostatic load (McEwen, 1998) has useful implications for the study of stress in pregnancy (cf. Shannon, King, & Powell Kennedy, 2007). Allostatic load is conceptualized as the cumulative biological effect of stress over time. If stressors over a lifetime pose wear and tear on the body’s systems, then we should study the level of “load” or past chronic strain a woman has had prior to pregnancy, not only her exposures during pregnancy. This dictates research designs that involve life history and preconception approaches together with biomarkers that capture chronic strain such as body mass index, waist–hip ratio, cholesterol, and blood pressure. The use of this and other ways of understanding how stress in the environment gets “under the skin” (Repetti, Taylor, & Seeman, 2002) and poses risk in pregnancy can offer both novel approaches and more focused hypotheses. Both broad theoretical approaches and narrower, well-specified conceptual models for the study of stress in PTB are needed at this juncture.

As noted above, existing models of stress and preterm birth are often simplistic regarding psychological processes. We suggest that the weak theoretical basis of inquiry on psychological and behavioral factors contributes to inability to test powerfully the meditational models linking prenatal stress to immune or HPA processes as mediators of effects of preterm birth. How does strong theory contribute to improving research on this topic? Theories can guide many of the issues that have plagued this area of research, such as definitions of stress, measurement or assessment tools, and low power in tests of mediation.

THEORETICAL SPECIFICITY REGARDING STRESS

Regarding the stress side (X variables), specificity means a focus on specific stressors, such as pregnancy anxiety or pregnancy-related stress, which has proven to be a consistent predictor of earlier delivery. Little attention has been directed to severity of anxiety symptoms, cognitive components, anxiety treatments, or other aspects of anxiety
that may be linked to physiological mediators and onset of
labor. Littleton, Brietkopf, and Berenson (2007) note that a
nearly exclusive focus has been on anxiety symptoms and
not on pathological levels of anxiety. Ross and McLean
(2006) discuss the prevalence of anxiety disorders in the
perinatal period, but studies on prevalence and implications
for fetal development and birth outcomes have not been
done. Various measures of pregnancy anxiety have also been
developed (e.g., Huizink, Mulder, & Buitelaar, 2004) but with
little theoretical basis and no tests of convergent validity to see if they assess the same concepts.

THEORETICAL SPECIFICITY REGARDING
BIOLOGICAL PROCESSES

The physiological state of pregnancy is complex and
dynamic. All of the potential mediational pathways link-
ing stress to preterm birth show predictable and dra-
matic changes in function during gestation. For example,
we and others have demonstrated that as pregnancy
progresses, women become less reactive both physiologi-
cally and psychologically to these exposures (de Weerth
& Buitelaar, 2005; Glynn et al., 2004). This suggests two
additional points of refinement to the study of the effects
of prenatal stress on preterm PTB. First, at the group level,
it suggests that as pregnancy progresses the strength of
association between a stress exposure and length of
gestation should be lessened. This is due to the fact that
as pregnancy progresses, the probability that a stress
exposure translates into a shortened gestation is dimin-
ished because both the physiological and psychological
response to stress are dampened. Second, at the level of
the individual, there are differences in the propensity to
show this dampening in stress responding. That is, there
is individual variability in the probability that an individu-
al woman shows reduced responding. It follows, then,
those women who remain relatively more sensitive
to stress will be more likely to deliver preterm, even in
the absence of differences in stress exposures. It further
follows that when these women are exposed, the con-
sequences will be more profound for them. There exist
empirical demonstrations that are consistent with both
of these premises. It has been shown that timing of stress
exposure during pregnancy is not uniform and that
early exposures may be more likely to produce a preterm
birth (Glynn et al., 2001; Lederman et al., 2004). Further,
as noted earlier, we have shown that women who do not
exhibit the expected decrease in reports of generalized
stress and anxiety during pregnancy are at increased risk
for PTB (Glynn et al., 2008).

MODERATORS OF THE STRESS–PRETERM
BIRTH ASSOCIATION

A further point is that we are not paying sufficient atten-
tion to potential moderating variables. Dispositional
factors appear to interact with or moderate the three pri-
mary factors. For example, genetic risk factors are gain-
ing increasing attention. There is growing evidence that
genetic susceptibility and gene–environment interac-
tions figure into models of early preterm birth (Cridner,
Whitehead, & Buus, 2005; Menon, Fortunato, Thorsen, &
Williams, 2006) via single gene variants, candidate genes,
and gene–environment interactions including stress.
This is a very important area for theory to incorporate.
Our group has been focusing on two sets of potential
moderators of the mediation of stress–preterm birth rela-
tions: (1) demographic and cultural factors and (2) sus-
ceptibility to stress. Demographic factors such as SES
and age are important as antecedents and modifiers of
behavior, immune function, and stress hormone activity.
Ethnic and cultural variables in particular are implicated
throughout the process and call for innovative approaches
and creativity. Specific models for specific ethnic groups
at risk, such as African Americans, may be the most use-
ful (Hogue & Bremner, 2005). Not only are specific stres-
sors relevant only to certain cultural groups in terms of
their ability to predict birth outcomes but it also appears
that the proposed biological mediators may exert stron-
ger or weaker relations with both the X or Z variables.
For example, Dominguez, Dunkel-Schetter, Glynn, and
Sandman (2008) have shown that lifetime exposures to
racism are predictive of restricted fetal growth but only
among African American women. Further, Holzman et al.
(2001) have shown that the threshold of CRH expos-
ure that is associated with preterm birth is lower among
African American women, and Glynn, Dunkel-Schetter,
Chicz-DeMet, Hobel, and Sandman (2007) have shown that
elevated prenatal cortisol is more likely be associated
with an accelerated CRH trajectory in African American
women than among White women.

As discussed previously, pregnancy affects the phys-
iological and psychological response to stress exposure,
and there are meaningful individual differences in these
processes during pregnancy (Glynn et al., 2008). Important
influences on these differences in susceptibility to stress
during pregnancy are lifetime exposures to either chronic
or traumatic stress and exposures during the preconcep-
tion period. Some women may enter pregnancy with a
latent vulnerability to stress that is expressed as gestation
progresses (Glynn et al., 2007). Exposure to stress in the
preconception period and over a woman's lifetime may
disregulate her physiology and increase risk of adverse
outcomes of pregnancy and for the child (Astone, Mira,
& Lynch, 2007; Lu & Halfon 2003; Noll et al., 2007).
The existence of such a preexisting vulnerability is consistent
with the view that lifelong exposures to stress among
women of ethnic minority status may increase the likeli-
hood of poor reproductive outcomes even before a preg-
nancy is conceived (Rich-Edwards & Grizzard, 2005)
and also that fetal programming may contribute to adult
reproductive health (Barker, 1998; Lu & Halfon, 2003).
These premises call for moderated mediational analy-
ses that to date have not been used in prenatal research.
The above differences suggest, for example, that among those women who are more vulnerable before pregnancy, stress exposures during pregnancy will have more potent effects on birth outcome.

Differences in environmental or genetic vulnerability to stress and the role of culture and ethnicity represent only two possible avenues for exploration of the moderated mediation of stress–PTB connection. However, it seems clear that complete models must consider the fact that the relations between stressors, mediators, and birth outcomes are best understood in the context of potential moderators of these X–Y–Z relations.

**OTHER EMERGING FRONTIERS**

There are a number of emerging areas in the study of preterm birth that pertain to this chapter. We spotlight only one of these very briefly, the effects of stress in pregnancy on development and health after delivery. There is enormous attention directed now to the topic of *fetal programming*, which refers broadly to the notion that many physiological systems are programmed in the womb in ways that influence later development and health throughout the life span. This notion is attributed mainly to Barker (1998), whose work pointed in the direction of adult health effects of perinatal events such as preterm birth. More recently, Gluckman and Hanson (2004) have contributed an elegant model of prenatal programming in the context of the Predictive Adaptive Response (PAR), which describes the process by which the developing organism draws from early experience to express a phenotype that maximizes fitness based on the expected future environment. It has been proposed that prenatal experience prepares the fetus for challenges in the postnatal environment and that it is the consistency (or lack of consistency) between the pre- and postnatal environments that determine the adaptability of the prenatal programming (Gluckman & Hanson, 2004; Hales & Barker, 2001; Horton, 2005). Thus, the adaptability of the response depends on the accuracy of the prediction. When the PAR does not match the postnatal environment, the mismatch results in reduced fitness (or disease states in the case of humans) (Gluckman & Hanson, 2004; Hales & Barker, 2001).

Empirical evidence supporting the link between prenatal experience and later health and development continues to accumulate and underscores the importance of prospective studies with human mothers and their fetuses and offspring. Coe and Lubach (2008) review animal and human studies indicating that the stimulation and priming occurring in utero guide optimal maturation of the nervous, endocrine, and immune systems and set regulatory set points governing physiology in adulthood. Talge, Neal, and Glover (2007) provide an excellent review of prospective studies on maternal stress in pregnancy and child emotional and cognitive effects, including ADHD, anxiety, and language delay, which supports clinically significant effects of maternal stress on child neurodevelopment (see also Beydoun & Saftlas, 2008). Research by our group has shown that maternal stress exposure reflected as changes in maternal affect and stress levels, as well as maternal HPA axis and placental hormones, influences the fetal environment with developmental consequences. We have shown that prenatal hormone exposures and also maternal psychological state during gestation predict fetal behavior and development (Class et al., 2008; Sandman et al., 2003), newborn neurodevelopment (Ellman, Dunkel-Schetter, Hobel, Glynn, & Sandman, 2008), and infant temperament and cognitive development (Davis et al., 2004, 2007; Davis, Glynn, Dunkel-Schetter, Hobel, & Sandman, 2005; Davis & Sandman, 2010). Importantly, each of these findings is independent of birth outcomes (length of gestation and birth weight), indicating direct fetal programming effects. The growing interest in the potential power of maternal stress factors in pregnancy to predict profoundly important outcomes in the offspring is hard to overestimate. It has the potential to strongly influence theory in both developmental and health psychology and to transform child and maternal health policies around the world.

In closing, we propose that a generation of new interdisciplinary biopsychosocial scientists is needed to work at multiple levels with multiple goals in mind to advance the study of stress in pregnancy. Past collaborations were among individuals of different disciplines, but the next decade will see more and more researchers trained in multiple disciplines of research. We hope this chapter informs and inspires those who might take up and carry this torch for the benefit of parents and children in the future.

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