Published in final edited form as:

J Midwifery Womens Health. 2009 ; 54(1): 8–17. doi:10.1016/j.jmwh.2008.08.001.

The Interaction Between Chronic Stress and Pregnancy: Preterm Birth from A Biobehavioral Perspective

Gwen Latendresse, CNM, PhD [assistant professor]

University of Utah, College of Nursing, Salt Lake City, UT.

Abstract

Women's health care providers are increasingly aware that chronic stressors—such as poverty, ongoing perceived stress and anxiety, intimate partner violence, and experiences of racism—are associated with an increased incidence of preterm birth in the United States. It is important to increase our understanding of the explanatory pathways involved in these associations. This article discusses the concepts of stress, chronic stress response, allostatic load, the physiology of labor initiation, and the pathophysiologic interactions that may contribute to the occurrence of chronic stress-related preterm birth. Implications for future research and interventions are explored.

Keywords

biobehavioral pathophysiology; chronic stress; pregnancy; premature birth

INTRODUCTION

Premature birth is the major contributor to infant morbidity and mortality, and often has serious long-term health consequences, such as cerebral palsy, blindness, and developmental difficulties that include cognitive, sensory, learning, and language deficits.¹ While no one major etiology has been identified, there is general agreement that there are multiple contributors to preterm birth (PTB).^{2,3} Significantly, idiopathic PTB accounts for approximately half of all PTBs (Figure 1, box on left).^{2,4}

In the past 4 decades, risk identification, early detection, and pharmaceutical interventions have made no impact in reducing the occurrence of PTB. Indeed, PTB has increased 31% since 1980.⁵ In the United States, the annual medical, educational, and lost productivity costs were estimated to be \$26.2 billion in 2005; \$5.8 billion for hospital costs alone.⁶⁻⁸

While there is a fairly clear understanding of and approach to management of the mechanical and medical contributors to the occurrence of PTB (i.e., multiple gestation, placental abruption, polyhydramnios, and infection) and medically induced PTB (i.e., due to placental insufficiency or severe pregnancy induced hypertension),⁹ the mechanisms involved in the psychosocial associations with PTB are much less clear. However, many researchers are beginning to address the maternal and fetal stress response and the cascade of physiologic events that may result in PTB, and are calling for others to do the same.^{8,10-16}

The goal of this article is to increase the clinician's understanding of how chronic stress may play a role in the occurrence of idiopathic PTB. To that end, attention will be given first to a

review of the concept and physiology of stress and the normal physiology of the initiation of labor. Subsequently, the interactions between pregnancy and chronic stress will be examined. The mechanical, medical, and infectious processes contributing to PTB have been given considerable attention by numerous authors, and will not be addressed here. A short glossary of terms is provided in Table 1 for the reader's convenience.

THE CONCEPT OF STRESS

The phenomenon of “stress,” in very general terms, is a physiologic response to psychological and physical demands and threats (stressors). An individual's unique characteristics (i.e., stressor appraisal, coping skills, disposition, etc.) and life circumstances (i.e., poverty, neighborhood environment, social support structures, etc.) also contribute to the individual's experience.¹⁷ The physiologic stress response has the goal of maintaining homeostasis, and the result is usually successful adaptation or resolution. However, negative health outcomes can result when the demands and threats substantially tax or overwhelm an individual's capacity to respond.¹⁸ For example, obesity, insulin resistance, cardiovascular disease, and metabolic syndrome are all potential long-term consequences of an altered metabolism that accompanies chronic activation of the physiologic stress response.¹⁹

It is also necessary to make a distinction between acute and chronic stress. Acute stress results in a response that is short-lived; effective resolution to the threat or demand is achieved. In contrast, chronic stress is of longer duration and/or lacks an effective resolution to the threat or demand. A heated argument with a spouse which results in problem solving and resolution is an example of acute stress; a psychological demand is met with a response that is short-lived and returns one to homeostasis. Repetitive, ongoing marital discord without resolution is an example of chronic stress; the threat is not resolved and does not allow one to return to homeostasis.

Cohen et al.¹⁷ have provided a helpful definition of stress, as follows: “when environmental demands [internal or external; real or imagined] tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease.” This definition represents a biobehavioral model of the stress process (Figure 2). The gray boxes have been added to Cohen's figure to provide specific examples of various contributors to the stress process.

However, the idea that stress causes physiologic change that in turn causes pathology would be a simplistic view of the stress phenomenon. As shown in Figure 2, aspects such as negative mood, depression, and anxiety can impact the appraisal of demands and threats. Furthermore, an individual's adaptive resources, such as coping skills and social support, are important elements in a comprehensive picture of the stress process.²⁰ A person with an adequate and supportive social network might appraise stressors in an optimistic light or use a problem-solving coping approach, with the knowledge that ready resources are available from friends and family members. Conversely, a person who is socially isolated or functioning within a violent or abusive environment may have a sense of hopelessness and negativity which can affect her appraisal of stressors. These are two simple examples of the complexity of stressor appraisal and response.

Moderators of stress, such as optimism, access to satisfactory and sufficient social supports, and adequate coping skills, have all been documented as “protective” (e.g., associated with reduction in perceived stress and with improved health outcomes in spite of the existence of “stressful” conditions and events).²¹⁻²⁴ In contrast, depression and anxiety are indicators of “distress,” and can both be considered as contributors to the stress response. These distressed states have dual roles in their contributions. They can affect one's appraisal of stressors in addition to activating the physiologic stress response independent of any other stressors.²⁵

Several studies support the premise that higher stress levels often lead to the development of depression and anxiety; therefore, distressed states may also be outcomes of chronic stress conditions rather than contributors to stress.²⁵

To summarize, the contributing and protective factors discussed above operate in a manner that can significantly impact an individual's appraisal and experience of stress, thereby altering the entire physiologic cascade of events that follow a stressful event or experience. Moreover, the mechanisms involved in the physiologic response in distressed states (i.e., depression and anxiety) may have additive, interactive, or independent effects on the stress response.

Finally, behavioral and lifestyle factors also add to the complexity of the stress response. Many individuals adopt behavior and lifestyle changes as coping strategies that may or may not be effective, or may even be harmful. Many of these changes can be viewed as beneficial in reducing stress and are associated with improved health outcomes (i.e., adequate sleep, exercise, and stress reduction methods). However, many can be harmful and contribute to adverse health outcomes (smoking, alcohol/drug use/abuse, poor diet, and inadequate sleep).

PHYSIOLOGIC STRESS RESPONSE: A CASCADE OF EVENTS

When an individual appraises stressors as demanding and/or threatening, two principal physiologic cascades occur. One involves the autonomic nervous system and the release of catecholamines, specifically norepinephrine and epinephrine. The second involves the hypothalamic-pituitary-adrenal (HPA) axis, whereby the release of corticotrophin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and cortisol predominate.

Both physiologic cascades originate in the brain.²⁶ While the precise mechanisms and feedback loops may vary according to differing stressors (i.e., psychological vs. physical challenges), CRH appears to play a central role in initiating/regulating the physiologic stress response. The release of CRH from the hypothalamus to the anterior pituitary occurs via a direct short vascular pathway (the hypophyseal portal vessels). This initiates a cascade of events that include the systemic release of ACTH, which subsequently signals the adrenal glands to release glucocorticoids (i.e., cortisol, which has powerful metabolic and anti-inflammatory effects). The secretion of CRH is also regulated via a negative feedback system; high cortisol levels signal the hypothalamus to decrease the release of CRH. The initiation of the HPA axis occurs in response to rich communication from the central nervous system (CNS), including the limbic system (involved in emotions, such as fear, anxiety, threat, grief, etc.).

Furthermore, activation of both the autonomic nervous system and the HPA axis results not only in physiological responses but also in behavioral changes, including decreased appetite and food intake, decreased sexual activity, increased feelings of anxiety and depression, and increased arousal/vigilance. In essence, activation of the HPA and the autonomic systems create the physiologic activation of the classic “fight or flight” responses in the body.²⁷

Short-term activation (acute stress) prompts the body's successful return to homeostasis. In contrast, long-term activation reflects either ongoing or repetitive stress, and/or an inability of the body to effectively respond to stressors. With chronic stress, the HPA axis and autonomic nervous system are repetitively activated, thus resulting in persistent physiologic effects. McEwen and Wingfield²⁸ describe this process of maintaining homeostasis as “allostasis,” whereby physiologic stability is achieved through continual change via the primary mediators of the HPA and autonomic nervous system (CRH, ACTH, cortisol, catecholamines, cytokines, etc.). Indeed, the concept of “allostatic load” has been introduced as a means for measuring and evaluating the cumulative effects of “wear and tear” on the body over a lifetime of exposure to the processes of allostasis. It has been suggested that the theory of allostasis and allostatic load is a more appropriate model for investigating stress-related health outcomes, including

perinatal outcomes, given the complexity and multifactorial nature of the stress response during childbearing.²⁹ Studies indicate that increasing allostatic load and allostatic overload place individuals at risk for adverse health outcomes, including PTB in pregnant women.^{11,30}

The physiologic, psychologic, and behavioral stress responses become quite relevant when juxtaposed with the mechanisms of labor initiation. Research implicates several of the stress response hormones (e.g., CRH, ACTH, and cortisol) as likely contributors to both term and PTB.³¹⁻³³ Conceptually, chronic stress may be an important component that explains at least one route to PTB. The physiologic stress response can interact with the physiology unique to a mother and fetus during pregnancy, including the mechanisms that initiate the labor process. Before moving into a discussion of this interaction, a review of the mechanisms of normal labor initiation may be helpful.

THE PHYSIOLOGY OF LABOR INITIATION

The initiation of normal term parturition is the result of an intricate interplay between the maternal, fetal, and placental endocrine, paracrine, and autocrine systems.³⁴ It involves complex positive and negative feedback systems, up and down regulation of cellular receptor sites, and dynamic chemical messenger systems. A cascade of events culminates in eventual maturation of the fetus and maternal uterine tissues and subsequent initiation of the labor process. A visual description of this fine-tuned process is presented in Figure 3.

The Role of Placental CRH

The presence of CRH in the maternal circulatory system during pregnancy is placental in origin and is secreted in increasing amounts over the course of pregnancy, beginning at approximately 16 weeks of gestation, and rising exponentially until the time of delivery.³⁵ This CRH produced by the placenta plays a central role in the physiology of term and PTB, including the length of gestation and the timing of birth.³⁶⁻³⁹ Furthermore, studies examining the role of placentally-derived maternal CRH levels, in relation to the length of gestation,^{38,40} have found that elevated levels of CRH early in gestation (16–20 weeks') is associated with a higher risk of PTB and precedes the occurrence of PTB by weeks or even months. These studies suggest that CRH is engaged in an intricate interaction with the endocrine and immune systems of the fetus, mother, and placenta.

Unlike the negative feedback system that regulates hypothalamic CRH, placental CRH functions under a positive feedback system, whereby cortisol (maternal and fetal) stimulates rather than inhibits the production of CRH in the placenta.^{33,35,41} Furthermore, an early study found that several maternal neural and adrenal "stress" hormones, including ACTH, vasopressin, oxytocin, and catecholamines stimulate production of CRH in the placenta.⁴¹ In other words, higher production of the chemical messengers involved in the stress response may result in higher production of CRH by the placenta. Although placental CRH may actually contribute to keeping the uterine muscle quiescent/relaxed during much of pregnancy, it appears to play another role at higher levels. Once a threshold level has been reached, CRH plays a significant role in the preparation for and the initiation of contractions and cervical remodeling required for labor to occur.⁴² These interactions are complex and not yet fully understood.

THE INTERACTION BETWEEN CHRONIC STRESS AND PREGNANCY

During the 1990s, research began to focus on the mechanisms of chronic stress-associated PTB in investigations that examined the psychosocial and neuroendocrine associations with PTB. Most published studies in the past 15 years have consistently documented associations between PTB and chronic maternal stress and/or psychosocial factors.^{3,11} Disparities in the occurrence

of PTB have also been described, including much higher rates in African American women and in women from lower socioeconomic environments.⁸ It has been proposed that such disparities may exist as a result of a lifetime of exposure to chronic stress (allostatic load)^{14, 43} rather than a predominant genetic predisposition. For example, a New York City study of PTB risk in various black subgroups of the population found substantial variation dependent on country of birth and ancestry group, with African Americans having the highest rate of PTB.⁴⁴ The conclusion of the study suggested that social and cultural context associated with ethnicity and nativity may contribute substantially more than sheer genetic predisposition, low socioeconomic status, or low education levels. Domestic violence, abuse, and posttraumatic stress disorder have also been linked to PTB.⁸

Several studies have identified relationships between “stress” hormones (i.e., ACTH and cortisol) and either an increased occurrence of PTB and/or increased maternal blood levels of CRH in pregnancy.^{32,33,45} More recently, Wadhwa et al.,⁴² in a prospective study of 232 pregnant women, found an association between elevated maternal plasma CRH levels at 33 weeks of gestation, and a 3.3-fold increase for spontaneous PTB (adjusted relative risk = 3.3; 95% confidence interval, 1.2–9.4).

A plausible explanation for the mechanisms of stress-related PTB is based on links between psychosocial stressors, physiologic stress response, and the cascade of events that occur in the mother, uterus, placenta, and fetus before birth. This cascade of events leading to PTB occurs regardless of the etiology. In other words, the pathophysiologic mechanisms that explain stress-related contributors and any of the other four major contributors to PTB (Figure 1) all occur somewhere along a common physiologic pathway to birth.

In the case of stress-associated PTB, it has been proposed that the neurohormonal effectors of the maternal stress response (and perhaps the fetus) contribute to an early and excessive placental CRH production, ultimately triggering the final cascade of events that culminates in PTB. Thus, a specific biobehavioral pathway pertinent to PTB may involve significant input from the maternal (and fetal) stress response. Investigations of the relationships between the three variables of 1) stress, 2) neuroendocrine markers (i.e., CRH), and 3) PTB together, however, are few. Only six such studies have been reported in the literature, and these are discussed below.

RELATIONSHIPS BETWEEN MATERNAL STRESS, NEUROENDOCRINE MARKERS, AND PTB

Six studies have examined PTB, neuroendocrine markers, and psychosocial factors together at the same time.^{40,46-50} While all six of these studies (Table 2) measured maternal CRH, two also measured cortisol,^{40,46} and one included measurements of ACTH.⁴⁰ Each of these studies included at least one behavioral, ethnic/racial, or psychosocial variable for measuring chronic stress contributors.

The results of all six of these studies lend support to the premise that one route to PTB may involve an interaction between the maternal stress response and gestational physiology. Women at highest risk for PTB were those who had higher blood levels of CRH, ACTH, and cortisol, higher perceived stress and/or anxiety scores, more risk-taking behavior, and lower socioeconomic status and education level. Furthermore, African American women and women with periods of fasting 13 hours or longer had higher CRH levels and were also more likely to deliver preterm.^{47,48} Pregnancy-related anxiety was also higher in African American women compared to white women.⁴⁹ Notably, perceived stress levels earlier in pregnancy (16–20 weeks) predicted higher CRH levels later in pregnancy (28–30 weeks).⁴⁰ Indeed, increased perceived stress and elevated CRH together appeared to explain 20% of the variance in

gestational age at birth.⁵⁰ In other words, higher perceived stress scores and higher levels of maternal CRH, when occurring together, predicted shorter gestational length.

The authors of all six studies arrived at the conclusion that a chronically activated maternal stress response may prematurely provoke the physiologic mechanisms that initiate the labor and delivery process. This conclusion also supports the theory of Challis et al.,⁵¹ who provide an extensive and thorough explanation of term and preterm mechanisms of labor, identifying the interrelationships between mother, fetus, and placenta that contribute to parturition. These mechanisms place the increase of placental CRH squarely at the center of an explanatory pathway for chronic stress-related PTB, directly implicating a chronic activation of the maternal stress response in the event. This biobehavioral relationship is depicted in Figure 4.

Study Limitations

The difficulty in comparing these studies lies in the fact that each uses different measures of “chronic stress.” For example, three of the six studies included a measure of women's perceived stress,^{40,47,50} two of which also included an anxiety measure,^{40,47} and one that included an assessment of periods of “fasting.”⁴⁷ One study measured only maternal pregnancy-related anxiety along with socioeconomic measures,⁴⁹ while another considered only racial background, along with education and Medicaid status,⁴⁸ as markers for chronic stress. Yet another study⁴⁶ reported a psychosocial assessment at 30 weeks of gestation that included “life events,” home duties, work demands, self-reported psychosocial stressors, health behaviors, and “risk-taking” (defined as “not wearing seat belts”) without providing information on precisely which instruments were used or the validity or reliability of the measures.

The use of a standardized, comprehensive measure of chronic stress is lacking in much of the research, which contributes to an inability to adequately evaluate the associations that exist between chronic stress, neurohormonal markers, and adverse pregnancy outcomes (i.e., PTB). Another common mistake in such studies has been to simply “count” the number of “stressful” events occurring in individuals’ lives. While this may be a practical and efficient approach, it often leads to research results that are not significant, ostensibly because it does not consider the complexity of individuals’ stress appraisals and responses. Very few studies include a comprehensive assessment of stress that uses psychometric, behavioral, and demographic measures while concurrently evaluating associations with biologic measures (i.e., CRH and ACTH) and PTB.

Indeed, the complexity of the phenomenon of chronic stress, the likelihood of genetic contributions, and the interactions occurring within the maternal-fetal-placental unit all provide compelling rationale for the use of biobehavioral, “life course,”¹⁴ and “allostatic load”^{29,43} perspectives when designing investigations of chronic stress-related PTB.

DISCUSSION, IMPLICATIONS, AND FUTURE DIRECTION

Prenatal healthcare providers routinely question expectant mothers regarding psychosocial factors during prenatal care, but are often at a loss for how to address such factors. What advice should be given to expectant mothers regarding the possible impact of chronic stress conditions on pregnancy and the unborn baby? How do providers tailor their approaches to addressing the unique set of circumstances presented by each expectant mother? What interventions are available or effective in reducing the risk of chronic stress-related PTB?

Unfortunately, while consistent data support the premise that chronic stress contributes to adverse reproductive outcomes such as PTB, clinicians are commonly left to intuitive approaches in dealing with them, given the current lack of evidence-based clinical direction. The March of Dimes Foundation advises women to reduce their stress levels during pregnancy

in an effort to reduce the risk of PTB.⁵² Others, such as Tiran and Chummun,⁵³ suggest a plethora of “complementary therapies” for stress reduction during pregnancy, including massage, aromatherapy, acupuncture, reflexology, and hypnotherapy, among others. However, there are no data to suggest that any of these mentioned recommendations and techniques actually reduce the occurrence of PTB. Such advice may be based on sound theoretical underpinnings of stress-related PTB, but it is exceptionally rare that any of these methods have been evaluated within the context of a well conducted research study.

While a few studies have evaluated stress reduction methods during pregnancy and have documented reductions in measures of maternal anxiety,⁵⁴ perceived stress,⁵⁵ and stress and depression,⁵⁶ few studies have evaluated these methods in relation to pregnancy outcomes. There are two notable exceptions. One prospective, intervention study reported by Mamelle⁵⁷ documented a reduction in the occurrence of PTB in women with threatened preterm labor who received psychological counseling during the prenatal period (7.2 % vs. 15.7% in the control group; $P < .02$). The second, a prospective, randomized, controlled study of the practice of yoga and pregnancy outcome by Narendran et al.,⁵⁸ reported a reduction in the PTB rate between a yoga intervention group and a control group (14% vs. 29%; $P = .0006$), as well as a reduction in intrauterine growth restriction (21% vs. 36%; $P = .003$). These results are certainly intriguing, and stand as sole examples of studies that investigate the impact of stress reduction techniques on pregnancy outcomes.

A third study deserves mention as well, in which stress reduction, per se, is not evaluated, but rather the study evaluated group prenatal care and pregnancy outcome.⁵⁹ Notably, in this randomized clinical trial, the incidence of PTB was significantly reduced in the women who participated in group prenatal care as opposed to women who received conventional individual prenatal care (9.8 vs. 13.8%; $P = .045$; odds ratio = 0.67). The authors of the report proposed that one mechanism explaining these results might be attributed to stress reduction, and thus a positive effect on the maternal and fetal endocrine stress responses that precipitate PTB.

The need for intervention studies seems quite apparent, given the paucity of such research. In addition to developing and evaluating intervention and prevention programs, however, more research must be directed toward identifying, evaluating, and further explaining the relationships that exist between chronic stress and PTB. Such studies could address populations of women with likely and/or known high levels of chronic stress, such as women exposed to discrimination, racism, oppression, war-torn environments, domestic violence, foreign and war-time military deployment, rape, refugee status, and childhood abuse, among others. Most of these populations of pregnant women have not been the subject of research investigations to date.

Until there is clear evidence-based clinical direction, prenatal care providers may certainly want to continue to assess for psychosocial indicators and to educate pregnant and preconceptional women regarding the research that documents the impact of chronic stress, without misleading them with recommendations of “untested” stress-reduction methods. At the same time, there have been no reports of adverse effects during pregnancy, of any of the common stress-reduction techniques available. At a minimum, women may feel less anxious and stressed by engaging in such methods, and could be reducing the potential for chronic stress/pregnancy interactions that lead to PTB, in addition to reducing their psychological distress. Therefore, it seems reasonable to give at least a “green light” to participation in stress reducing activities.

The majority of women who experience chronic stress, however, do not go on to deliver a preterm infant. This likely reflects the multiplicity of factors that contribute to the occurrence of PTB, including a genetic component that may contribute to a woman's susceptibility to the

effects of her individual stress response.⁶⁰ Given the complexity of the human stress response, which includes this genetic component and an individual's unique stress response and life course, it becomes clear that applying theories of allostasis and allostatic load to investigations of chronic stress and pregnancy outcomes could facilitate such studies. For example, an accelerated chromosomal telomere shortening (a marker of cellular aging) has been associated with higher levels of perceived stress in women caring for their chronically ill children.⁶¹ The suggested implication is that chronic stress contributes to allostatic load, thus to cellular aging and subsequent risk of dysfunction and disease typically associated with increasing chronological age. The identification of such markers within the context of pregnancy, and in relation to pregnancy outcome, could be illuminating.

CONCLUSION

A large body of evidence supports the premise that the risk of PTB is increased when maternal chronic stress is present in some women. In addition, research implicates the interaction between the maternal stress response and the physiology of pregnancy and parturition, as one of the pathophysiologic mechanisms explaining PTB. Investigations that use biobehavioral, life course, or allostatic load perspectives have potential to provide valuable input into exploring the phenomenon of stress-related PTB, and into development of prevention and intervention programs, such as stress reduction. With more than half a million babies born prematurely in the United States each year, a deeply concerning disparity existing among minority and socioeconomically disadvantaged women,⁵ and an increasing PTB rate, it is time for the conduct of research using novel approaches and interventions.

Acknowledgements

Supported by the National Institute of Nursing Research, National Institute of Health (1 F31 NR010046-01), the March of Dimes Foundation, and the American College of Nurse-Midwives Foundation, Inc.

REFERENCES

1. Allen MC. Neurodevelopmental outcomes of preterm infants. *Curr Opin Neurol* 2008;21:123–8. [PubMed: 18317268]
2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84. [PubMed: 18177778]
3. Steer P. The epidemiology of preterm labour. *BJOG* 2005;112(Suppl 1):1–3. [PubMed: 15715585]
4. Moutquin JM. Classification and heterogeneity of preterm birth. *BJOG* 2003;110(Suppl 20):30–3. [PubMed: 12763108]
5. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: Final data for 2005. *Natl Vital Stat Rep* 2007;56:1–103. [PubMed: 18277471]
6. Petrou S. The economic consequences of preterm birth during the first 10 years of life. *BJOG* 2005;112 (Suppl 1):10–5. [PubMed: 15715587]
7. Russell RB, Green NS, Steiner CA, Meikle S, Howse JL, Poschman K, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. *Pediatrics* 2007;120:e1–9. [PubMed: 17606536]
8. Behrman, RE.; Stith Butler, A., editors. Preterm birth: Causes, consequences, and prevention. National Academies Press; Washington, DC: 2007.
9. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet* 2008;371:164–75. [PubMed: 18191687]
10. Hobel C, Culhane J. Role of psychosocial and nutritional stress on poor pregnancy outcome. *J Nutr* 2003;133:1709S–17S. [PubMed: 12730488]
11. Rich-Edwards JW, Grizzard TA. Psychosocial stress and neuroendocrine mechanisms in preterm delivery. *Am J Obstet Gynecol* 2005;192:S30–5. [PubMed: 15891710]

12. Ruiz RJ, Fullerton J, Dudley DJ. The interrelationship of maternal stress, endocrine factors and inflammation on gestational length. *Obstet Gynecol Surv* 2003;58:415–28. [PubMed: 12775946]
13. Wadhwa PD. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. *Psychoneuroendocrinology* 2005;30:724–43. [PubMed: 15919579]
14. Hogue CJ, Bremner JD. Stress model for research into preterm delivery among black women. *Am J Obstet Gynecol* 2005;192:S47–55. [PubMed: 15891712]
15. Hogue CJ, Hoffman S, Hatch MC. Stress and preterm delivery: A conceptual framework. *Paediatr Perinat Epidemiol* 2001;15(Suppl 2):30–40. [PubMed: 11520398]
16. Green NS, Damus K, Simpson JL, Iams J, Reece EA, Hobel CJ, et al. Research agenda for preterm birth: Recommendations from the March of Dimes. *Am J Obstet Gynecol* 2005;193(3 Part 1):626–35. [PubMed: 16150253]
17. Cohen, S.; Kessler, RC.; Gordon, LU. *Measuring stress: A guide for health and social scientists.* Oxford University Press; New York: 1997.
18. Shelby, J.; McCance, KL. Stress and disease.. In: McCance, KL.; Huether, SE., editors. *Pathophysiology: The biologic basis for disease in adults and children.* Vol. 5th ed.. Elsevier Health Sciences; New York: 2006. p. 311
19. Kyrou I, Chrousos GP, Tsigos C. Stress, visceral obesity, and metabolic complications. *Ann N Y Acad Sci* 2006;1083:77–110. [PubMed: 17148735]
20. Moos R, Holahan C. Dispositional and contextual perspectives on coping: Toward an integrative framework. *J Clin Psychol* 2003;59:1387–403. [PubMed: 14618606]
21. Steptoe A, O'Donnell K, Marmot M, Wardle J. Positive affect and psychosocial processes related to health. *Br J Psychol* 2007;99(Part 2):211–27. [PubMed: 17599784]
22. Smith TW, MacKenzie J. Personality and risk of physical illness. *Annu Rev Clin Psychol* 2006;2:435–67. [PubMed: 17716078]
23. Taylor SE, Stanton AL. Coping resources, coping processes, and mental health. *Annu Rev Clin Psychol* 2007;3:377–401. [PubMed: 17716061]
24. Uchino, B. Pathways linking social support to health outcomes.. In: Uchino, B., editor. *Social support and physical health: Understanding the health consequences of relationships.* Yale University Press; New Haven, CT: 2004. p. 109-44.
25. Chrousos G. Stressors, stress, and neuroendocrine integration of the adaptive response. *Ann N Y Acad Sci* 1998;851:311–35. [PubMed: 9668623]
26. Johnson E, Kamilaris T, Chrousos G, Gold P. Mechanisms of stress: A dynamic overview of hormonal and behavioral homeostasis. *Neurosci Biobehav Rev* 1992;16:115–30. [PubMed: 1630726]
27. Chrousos GP. The HPA axis and the stress response. *Endocr Res* 2000;26:513–4. [PubMed: 11196421]
28. McEwen B, Wingfield J. The concept of allostasis in biology and biomedicine. *Horm Behav* 2003;43:2–15. [PubMed: 12614627]
29. Shannon M, King TL, Kennedy HP. Allostasis: A theoretical framework for understanding and evaluating perinatal health outcomes. *J Obstet Gynecol Neonatal Nurs* 2007;36:125–34.
30. McEwen B. Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev* 2007;87:873–904. [PubMed: 17615391]
31. Yeast JD, Lu G. Biochemical markers for the prediction of preterm delivery. *Clin Perinatol* 2007;34:573–86. [PubMed: 18063106]
32. Makrigiannakis A, Semmler M, Briesse V, Eckerle H, Minas V, Mylonas I, et al. Maternal serum corticotropin-releasing hormone and ACTH levels as predictive markers of premature labor. *Int J Gynaecol Obstet* 2007;97:115–9. [PubMed: 17368647]
33. Sandman CA, Glynn L, Schetter CD, Wadhwa P, Garite T, Chiciz-DeMet A, et al. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): Priming the placental clock. *Peptides* 2006;27:1457–63. [PubMed: 16309788]
34. Norwitz ER, Robinson JN, Challis JR. The control of labor. *N Engl J Med* 1999;341:660–6. [PubMed: 10460818]
35. Smith R, Mesiano S, McGrath S. Hormone trajectories leading to human birth. *Regul Pept* 2002;108:159–64. [PubMed: 12220740]

36. Challis JRG, Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. *Endocr Rev* 2000;21:514–50. [PubMed: 11041447]
37. Majzoub JA, McGregor JA, Lockwood CJ, Smith R, Taggart MS, Schulkin J. A central theory of preterm and term labor: putative role for corticotropin-releasing hormone. *Am J Obstet Gynecol* 1999;180(1 Part 3):S232–41. [PubMed: 9914624]
38. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. *Nat Med* 1995;1:460–3. [PubMed: 7585095]
39. Reis F, Fadalti M, Florio P, Petraglia F. Putative role of placental corticotropin-releasing factor in the mechanisms of human parturition. *J Soc Gynecol Invest* 1999;6:109–19.
40. Hobel C, Dunkel-Schetter C, Roesch SC, Castro LC, Arora CP. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in pre-term delivery. *Am J Obstet Gynecol* 1999;180(1 Part 3):S257–63. [PubMed: 9914629]
41. Hillhouse EW, Grammatopoulos DK. Role of stress peptides during human pregnancy and labour. *Reproduction* 2002;124:323–9. [PubMed: 12201805]
42. Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: A prospective investigation. *Am J Obstet Gynecol* 2004;191:1063–9. [PubMed: 15507922]
43. Lu MC, Chen B. Racial and ethnic disparities in preterm birth: The role of stressful life events. *Am J Obstet Gynecol* 2004;191:691–9. [PubMed: 15467527]
44. Howard DL, Marshall SS, Kaufman JS, Savitz DA. Variations in low birth weight and preterm delivery among blacks in relation to ancestry and nativity: New York City, 1998–2002. *Pediatrics* 2006;118:e1399–405. [PubMed: 17079541]
45. McGrath S, McLean M, Smith D, Bisits A, Giles W, Smith R. Maternal plasma corticotropin-releasing hormone trajectories vary depending on the cause of preterm delivery. *Am J Obstet Gynecol* 2002;186:257–60. [PubMed: 11854646]
46. Erickson K, Thorsen P, Chrousos G, Grigoriadis DE, Khongsaly O, McGregor J, et al. Preterm birth: Associated neuroendocrine, medical, and behavioral risk factors. *J Clin Endocrinol Metab* 2001;86:2544–52. [PubMed: 11397853]
47. Herrmann TS, Siega-Riz AM, Hobel CJ, Aurora C, Dunkel-Schetter C. Prolonged periods without food intake during pregnancy increase risk for elevated maternal corticotropin-releasing hormone concentrations. *Am J Obstet Gynecol* 2001;185:403–12. [PubMed: 11518900]
48. Holzman C, Jetton J, Siler-Khodr T, Fisher R, Rip T. Second trimester corticotropin-releasing hormone levels in relation to preterm delivery and ethnicity. *Obstet Gynecol* 2001;97:657–63. [PubMed: 11339911]
49. Mancuso RA, Schetter CD, Rini CM, Roesch SC, Hobel CJ. Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. *Psychosom Med* 2004;66:762–9. [PubMed: 15385704]
50. Ruiz RJ, Fullerton J, Brown CE, Dudley DJ. Predicting risk of preterm birth: The roles of stress, clinical risk factors, and corticotropin-releasing hormone. *Biol Res Nurs* 2002;4:54–64. [PubMed: 12363283]
51. Challis JR. Maternal corticotropin-releasing hormone, fetal growth, and preterm birth. *Am J Obstet Gynecol* 2004;191:1059–60. [PubMed: 15507920]
52. March of Dimes Web site. Pregnancy and newborn health education center. [March 3, 2008]. Available from: www.marchofdimes.com/pnhec/159_527.asp
53. Tiran D, Chummun H. Complementary therapies to reduce physiological stress in pregnancy. *Complement Ther Nurs Midwifery* 2004;10:162–7. [PubMed: 15279857]
54. Teixeira J, Martin D, Prendiville O, Glover V. The effects of acute relaxation on indices of anxiety during pregnancy. *J Psychosom Obstet Gynecol* 2005;26:271–6.
55. Wesley Y. Reduce stress: A stress reduction project for pregnant black women. *J Cult Divers* 2006;13:208–16. [PubMed: 17338491]
56. Urizar GG Jr, Milazzo M, Le HN, Delucchi K, Sotelo R, Muñoz R. Impact of stress reduction instructions on stress and cortisol levels during pregnancy. *Biol Psychol* 2004;67:275–82. [PubMed: 15294386]

57. Mamelle N. Psychological prevention of early pre-term birth: A reliable benefit. *Biol Neonate* 2001;79:268–73. [PubMed: 11275664]
58. Narendran S, Nagarathna R, Narendran V, Gunasheela S, Nagendra HRR. Efficacy of yoga on pregnancy outcome. *J Altern Complement Med* 2005;11:237–44. [PubMed: 15865489]
59. Ickovics JR, Kershaw TS, Westdahl C, Magriples U, Massey Z, Reynolds H, et al. Group prenatal care and perinatal outcomes: A randomized controlled trial. *Obstet Gynecol* 2007;110(2 Part 1):330–9. [PubMed: 17666608]
60. Crider KS, Whitehead N, Buus RM. Genetic variation associated with preterm birth: A HuGE review. *Genet Med* 2005;7:593–604. [PubMed: 16301860]
61. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 2004;101:17312–5. [PubMed: 15574496]

Figure 1.
 Contributors to preterm birth. DM = diabetes mellitus; HTN = hypertension; PPROM = premature preterm rupture of membranes.

Figure 2. Heuristic model of the stress process. Adapted and reprinted from Cohen et al.¹⁷ by permission of Oxford University Press, Inc.

Figure 3. Proposed mechanism of labor induction at term. Reprinted with permission from Norwitz et al.³⁴ Copyright© 1999 Massachusetts Medical Society. All rights reserved. CRH = corticotropin-releasing hormone; DHEAS = dehydroepiandrosterone sulfate; SROM = spontaneous rupture of membranes.

Biobehavioral Pathway from Chronic Stress to Preterm Birth

Figure 4. Biobehavioral pathway from chronic stress to preterm birth. CRH = corticotrophin-releasing hormone.

Table 1
Glossary of Terms

<p>Allostasis: A physiologic process that maintains homeostasis via stress mediators (corticotrophin-releasing hormone, Cortisol, catecholamines, cytokines, etc.).²⁸</p> <p>Allostatic Load: The cumulative wear and tear, physiologically, on the body as a result of chronic exposure to the stress response.²⁸</p> <p>Autocrine: The secreting cells and the target cells are the same; the chemical messengers have effect only on the cells that secreted them. Prostaglandins may function in this manner to degrade cervical tissues at or near the time of labor.¹⁸</p> <p>Biobehavioral Perspective: Examining health conditions and events by using biological, behavioral, psychological, and social measures in order to obtain a comprehensive picture of the event or condition.</p> <p>Endocrine: Chemical messengers are secreted into the bloodstream and travel to distant target cells. Cortisol is an example.¹⁸</p> <p>Idiopathic: Arising spontaneously or from an obscure or unknown cause. Medically induced or explained PTB is not idiopathic.</p> <p>Life Course Perspective: Similar to the concept of allostatic load; the events, conditions, and individual responses over an entire lifetime are felt to impact one's later health outcomes.¹⁵</p> <p>Paracrine: Chemical messengers are secreted locally with effects on neighboring target cells. Placental CRH functions in this manner.¹⁸</p> <p>Stress: "when environmental demands" (internal or external; real or imagined) "tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease."¹⁷</p>

Table 2

Associations Between Maternal CRH Levels, Psychosocial/Behavioral Measures, and Preterm Birth

Study, Design, and Sample Size	Neuroendocrine and Psychosocial Measures	Outcome Measures	Results ^a
Erickson et al. ⁴⁶ (2001); prospective, longitudinal; n = 59 PTB and n = 166 term	Maternal CRH and cortisol, self-reported life events, home and work demands, health and risk-taking behaviors, SES	PTB (yes or no)	Low education level (OR = 2.93; CI = 1.1–7.8); risk-taking behavior (OR = 2.83; CI = 1.16–6.9); high CRH level (OR = 2.36; CI = 1.21–4.6); previous PTB (OR = 7.56; CI = 2.9–19.9)
Herrmann et al. ⁴⁷ (2001); prospective, longitudinal; n = 237	Maternal CRH, self-reported PSS, PSA, life events, SES, ethnicity, and periods of fasting ≥ 13 hrs	High maternal CRH levels (yes or no)	≥ 13 hrs fasting (RR = 2.0; CI = 0.9–4.2)
Hobel et al. ⁴⁰ (1999); prospective, case-control; n = 524; 18 PTB, 18 term	Maternal CRH, ACTH, and cortisol, self-reported PSS and PSA	Maternal CRH levels	Maternal age predicted CRH (β = .40); PSS scores at 18–20 wks GA predicted changes in CRH (β = .35); correlations (in PTB group): PSS and CRH (r = 0.48); maternal age and CRH (r = –0.53); PTB group vs. term group: higher CRH, ACTH, and cortisol
Holzman et al. ⁴⁸ (2001); prospective, case-control; n = 3327; 241 PTB, 244 term	Maternal CRH, race/ethnicity, SES, demographics	PTB <35 wks GA	CRH >1.5 MoM in EA women (OR = 2.3; CI = 1.1–5.1); CRH >1.5 MoM in AA women (OR = 5.0; CI = 1.8–13.3); CRH levels: PTB <35 wks vs. term birth in AA women (73.6 pg/mL vs. 50.7 pg/mL)
Mancuso et al. ⁴⁹ (2004); prospective, longitudinal; n = 282	Maternal CRH, PSA, SES, parity, PTB vs. term	GA (in wks)	PSA at 28–30 wks predicted GA at birth (β = –.14); PSA for AA vs. EA women (12.02 vs. 10.26); CRH levels at 18–20 wks GA in PTB vs. term birth (25.6 vs. 7.74) and at 28–30 wks GA (316.74 vs. 244.01); correlations: CRH and GA (r = –0.37 to 0.41); PSA & GA (r = –0.19); CRH and PSA (r = 0.15)
Ruiz et al. ⁵⁰ (2002); prospective, longitudinal; n = 78; 6 PTL and PTB, 17 PTL and term, 53 term	Maternal CRH, PSS, smoking, ethnicity, PTB vs. term	GA (in wks)	CRH, stress, PTL, and ethnic group predict GA at birth (r^2 = 0.273); CRH and stress alone predict GA at birth (r^2 = 0.20) PTB vs. term birth CRH levels (5.01 $\pm$ 1.25 pg/mL vs. 3.84 $\pm$ 0.61 pg/mL) at 23–26 wks GA; white vs. Hispanic CRH levels (4.51 $\pm$ 0.83 pg/mL vs. 3.91 $\pm$ 0.65 pg/mL) at 23–26 wks GA; correlations: PSS and GA (r = 0.17; P = .09); PSS decrease and GA (r = 0.43)

AA = African American; ACTH = adrenocorticotrophic hormone; CI = 95% confidence interval; CRH = corticotropin-releasing hormone; EA = European American; GA = gestational age; MoM = multiple of the median; OR = odds ratio; pg/mL = picograms/milliliter; PSA = pregnancy-specific anxiety; PSS = Perceived Stress Scale; PTB = preterm birth; PTL = preterm labor; RR = relative risk; SD = standard deviation; SES = socioeconomic status.

^a Only statistically significant results are being reported, unless otherwise specified ($P < .05$).