Advances in Nursing Science
Vol. 28, No. 4, pp. 345–355

Effects of Maternal Prenatal Stress on Infant Outcomes
A Synthesis of the Literature

R. Jeanne Ruiz, PhD, RN, WHNP; Kay C. Avant, PhD, RN, FAAN

There is growing evidence that maternal prenatal stress may be hazardous to infant health. Changes in maternal hormonal and immune function as a result of stress may adversely affect the immune function and neurodevelopment of the fetus. Prenatal stress in the mother may produce lasting effects on the (1) infant's health status, (2) development and function of the infant's immune system, and (3) neurocognitive development of the infant. This article provides a synthesis of current human and animal literature on the effects of maternal prenatal stress on the developing fetus and the infant, with the resulting model evolving out of the framework of psychoneuroimmunology. The intent of the authors is an integrative review. The authors examined the following research question: What effect does maternal prenatal stress have on infants' immune development and neurodevelopment? All relevant studies were reviewed with no exclusion criteria. Major databases (CINAHL, MEDLINE, PsychINFO) were searched using a combination of the following key words: prenatal stress, cytokines, thymus, and infant neurodevelopment. **Key words:** *infant outcomes*, *prenatal stress*, *psychoneuroimmunology*, *theoretical model*

THE prenatal period is a critical period for the development of the infant's brain and immunity. As such, it is a vulnerable time for anything that may disturb homeostasis and development, such as stress. Recent investigations have linked effects of prenatal stress in the mother to perinatal outcomes for the infant, specifically birth weight and gestational age.[1–3] However, animal studies, as well as preliminary studies in humans, suggest that the effects of prenatal stress may continue long after the baby is born.[4–9] There may be sensitive periods for stressors and critical developmental set points during fetal life that program the neuroendocrine and immune functions in childhood and even into adulthood. In fact, prenatal stress in the mother may produce lasting effects on the (1) infant's health status, (2) development and function of the infant's immune system, and (3) neurocognitive development of the infant. The immaturity of the immune system of the fetus and the young infant makes both the fetus and the infant particularly vulnerable to disease. Inadequate immune responses in an infant may result in poorer health, more clinic or emergency visits, increased costs for the families, and strain on the healthcare system as a whole.

In the last 30 years, scientists have studied signals and routes linking psychosocial stressors and physical stressors to endocrine and immune responses.[10,11] Nevertheless, the link between maternal psychosocial stressors and children's immunity has not been well described. The link has been better studied in animals than in humans, leaving gaps as to the extent of the implications in humans. Recently, investigators have begun to examine the effects of maternal prenatal psychosocial stressors on neurocognitive development in

From the University of Texas Medical Branch, Galveston (Dr Ruiz); and the School of Nursing, The University of Texas at Austin, Austin (Dr Avant). Dr Avant is now with the School of Nursing, The University of Texas Health Science, San Antonio.

Corresponding author: Kay C. Avant, PhD, RN, FAAN, School of Nursing, The University of Texas Health Science Center-San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (e-mail: kayavant@aol.com).

the human infant. This article will provide a synthesis of the current human and animal literature on the effects of prenatal stress on the developing fetus and infant, with the resulting model evolving out of the framework of psychoneuroimmunology.[10] The authors will propose both nursing implications and the need for future research on the basis of this synthesis.

Psychoneuroimmunology is the study of the interactions among one's psychological state (psycho), neuroendocrine system (neuro), and immune system (immunology),[10,11] Psychoneuroimmunology provides a framework for examining the relationships between behavioral and biological phenomena and their influence on health outcomes. In this case, the relationship is between psychological stress in the mother and the resulting maternal biological response, with the outcomes on the immune system and neurocognitive development in the infant. The term *stress* is used to describe any physical or psychological challenge that threatens, or has the potential to threaten, the stability of the internal milieu of the organism (homeostasis).[3]

In the aforementioned biological response to stress, the neuroendocrine and immune systems play a major role in adaptation to stress. The immune, endocrine, and nervous systems communicate with each other through short and long communication loops.[11] Activation of the stress system leads to suppression of the immune system, primarily via glucocorticoid-induced changes. Production of cytokines and mediators of inflammation is decreased, and their action on target T cells is diminished. In turn, the immune system may activate the stress system by cytokine mediators of inflammation to stimulate corticotropin-releasing hormone (CRH), a 41-amino acid neuropeptide that regulates the physiological responses to stress and inflammation. A full negative feedback system occurs between the hypothalamic-pituitary-adrenal (HPA) axis of the stress system and the immune/inflammatory response.[11]

MATERNAL PRENATAL STRESS

Stress is conceptualized in a variety of ways, with chronic stress being but one type of stress. Chronic stress has the greatest effect on immunity. Chronic stressors[12] are described as permeating a person's life, forcing that individual to reorganize his/her identity and/or social role. Chronic stressors are characterized by uncertainty regarding the time at which they will end. In Segerstrom and Miller's meta-analysis[12] of studies completed in a variety of individual situations, chronic stressors were found to be associated with the most global immunosuppression, initially in cellular immunity, and then in immune function more broadly. These findings have particular implications for pregnant women, especially those belonging to ethnic minorities and low-income women who are often at risk for chronic stress. For Hispanics, for instance, birth outcomes deteriorate as the number of years for which they have lived in America increases,[13] implying that attempting to adapt to a new culture may be a chronic stressor.

Authors reporting one study[14] present evidence that chronic stress in healthy adults impairs the immune system's response to anti-inflammatory signals and pro-inflammatory cytokines, thus regulating the inflammatory response. In one of the few studies examining the effects of stress on the immune system in pregnancy, a cross-sectional investigation of 72 pregnant women[15] reported that high levels of maternal psychological stress and low levels of social support were significantly associated with depression of lymphocyte activity in the mother.

Conceptually, anxiety is closely related to stress. *Anxiety* may be defined as the psychological consequence of exposure to real or imagined stress.[16] High trait anxiety (personality related) may increase the psychological response to stress.[17] Anxiety has been related to preterm birth but not to low birth weight (LBW) in one study.[18] In another study, both depression and anxiety were found to be associated with LBW.[19] In the study of McCool

et al,[19] trait anxiety scores at less than 20 weeks were higher for subjects who delivered either preterm or postterm. State/trait anxiety measured at 32 to 36 weeks gestation was related to gestational age at birth.

Some studies have used stress and anxiety as a composite variable, combining stress and anxiety to represent one concept.[20] These studies found that the composite of the stress variable was related to LBW and preterm birth. However, when individual measures of anxiety and depression were used, the relationships were no longer present.[20] Lobel and Dunkel-Schetter[21] did repeated testing of stress throughout pregnancy using measures of perceived stress, life events, and state anxiety. The composite variable of psychosocial distress measured the predicted gestational length when birth weight, parity, substance use, and medical risk were controlled. The composite variable of anxiety, perceived stress, and life events seemed to reflect chronic stress, now implicated in adverse health effects. In a study by Rini et al,[22] structural equation modeling was used to sort out the effects of state anxiety and pregnancy-related anxiety on gestational length and birth weight. Both types of anxiety predicted gestational length. Stress and psychological resources mediated ethnic differences in gestational age and birth weight.

A common consequence of stress is depression. Depressive symptoms are common in pregnancy, especially in lower socioeconomic status women. Hoffman and Hatch[23] suggest that depressive mood may be associated with poor fetal growth among lower socioeconomic status women. Depression has also been linked to the stress response of the HPA axis, specifically CRH and cortisol levels in pregnancy[24] as well as in the nonpregnant state.[11] Changes in both cortisol and CRH levels have been found to be associated with depression and antisocial behavior in pregnant adolescents.[24] In one study, depression and CRH levels were negatively associated.[25] In the same study, CRH levels were positively associated with levels of the cytokine interleukin 1 (IL-1). However, the sample size of preterm infants was too small to make any conclusions regarding the links of CRH, depression, IL-1, and LBW or premature birth. Other studies have found that CRH and serotonin form circuits in the brain, with both being implicated in the pathophysiology of major depression and suicide.[26]

EFFECTS OF PRENATAL STRESS ON MATERNAL ENDOCRINE FACTORS AND MATERNAL IMMUNE FACTORS

A major component of the response to stress is CRH in the hypothalamus, which regulates the peripheral activities of the HPA axis. In pregnancy, very early in gestation, the placenta produces hormones and cytokines and appears to function in a manner similar to HPA target systems. Placental CRH is identical to hypothalamic CRH in structure[27] and increases exponentially over gestation, resulting in its release into the maternal and fetal compartments. The physiology of placental CRH illustrates that the placenta acts as a sensory and effector organ for the fetus. Activation of the HPA axis by CRH results in the systemic elevation of glucocorticoids (cortisol). Glucocorticoids act in concert to maintain or effect a return to the state of homeostasis.[11] Placental CRH is thought to regulate fetal growth by effecting placental perfusion and fetal cortisol production. Fetal cortisol is essential for organ growth and maturation and has a positive feedback loop with CRH. Wadhwa and colleagues[28] reported significant associations between maternal psychosocial stress and 2 effectors of placental CRH (maternal ACTH [adrenocorticotropic hormone] and cortisol) in the early third trimester of gestation. Therefore, CRH and cortisol are key endocrine factors with the stress response in regulating maternal fetal health.

A stressor may also be an immune challenge that threatens homeostasis. Certain cytokines, such as tumor necrosis factor-α (TNF-α), IL-1, and IL-6, activate the stress system in vivo.[29] Stress that is associated with an immune challenge has been called *immune or*

inflammatory stress, and, like other forms of stress, is coordinated by the central stress system and its peripheral components. The observations that stress hormones, particularly glucocorticoids, inhibit lymphocyte/leukocyte proliferation, migration, and cytotoxicity, as well as the secretion of certain cytokines, such as IL-2 and interferon-gamma (INF-γ), led to the initial conclusion that stress was, in general, immunosuppressive.[3] More recent research, however, suggests that stress-induced concentrations of glucocorticoids and catecholamines may influence the immune response in a more complex way.

Immune responses are controlled by (*a*) antigen-presenting cells, such as monocytes and macrophages, which are components of innate immunity, and (*b*) T-helper (Th) lymphocyte subclasses Th1 and Th2, which are components of acquired or adaptive immunity. Th1 cells promote cellular immunity, whereas Th2 cells promote humoral immunity. Naive $CD4^+$ (or T-cell subsets that are antigen-inexperienced) Th0 cells serve as precursors of Th1 and Th2 cells. Cytokines produced by the cells of the innate immune system (monocytes and macrophages) are among the most important factors influencing differentiation of TH0 cells toward the Th1 or Th2 subset, which drive cellular and humoral immune responses. Th1 and Th2 responses are mutually inhibitory.[3] Evidence over the past few years strongly suggests that stress hormones differentially regulate Th1/Th2 patterns and type 1/type 2 cytokine secretion, thereby potentially altering the balance between these 2 arms of acquired immune responses.[30] Successful pregnancy requires a shift in the maternal cytokine ratio from predominantly Th1 (pro-inflammatory) to Th2 (anti-inflammatory).[31] Recurrent pregnancy loss has been associated with failure of this shift in cytokines.[32]

Investigators have found that the physiologic response to chronic stress in pregnancy includes significant changes in the maternal immune response, affecting cytokines.[2] When the maternal cytokines cross the placenta, they can affect the fetus. IL-6 and IL-8 receptors are found in a wide variety of fetal tissues, including brain stem and cerebellum.[33] This early binding and activation in the fetal brain may permanently alter later interactions and can have significant effects on the central nervous system and immune function.

MATERNAL PRENATAL STRESS AND NEUROCOGNITIVE DEVELOPMENT OF THE INFANT

Neuroscience studies indicate that the hippocampus appears to be adversely affected by stress during early development.[34] The hippocampal pyramidal neurons contain a high concentration of glucocorticoid receptors that are sensitive either to hypercortisolemia caused by severe stress or to exposure to exogenous glucocorticoids.[35] Some researchers suggest that prenatal stress enhances the release of maternal stress hormones, and these hormones are able to enter the fetal circulation. In turn, they affect fetal hippocampal ontogeny by downregulating glucocorticoid receptors and/or exerting neurotoxic effects on hippocampal cells.[34]

The hippocampus and its connecting fibers within the other limbic and paralimbic structures are particularly important in the development of associative memory. Hippocampal insufficiency causes disruption in the performance of associative memory, spatial memory tasks, and procedural (or reference) memory.[36] The limbic system also mediates the development of conditioned responses and, in the absence of one-to-one reinforcement schedules, mediates operant learning paradigms. Damage to the medial temporal lobe, amygdala, and its connecting fibers typically results in difficulties in the formation of new memories and in affective rage-like behaviors.[37] The hippocampal region functionally interconnects with the frontal lobes that regulate executive functioning activities: (1) volition, (2) planning, (3) purposive action, and (4) effective performance. Damage to the frontal lobes, that is, executive functioning, impedes the input, storage, and

integration of data.[37] Prenatal stress research involving animal models has shown impairments in the areas of acquiring discriminative learning, shifting problem-solving strategies, and demonstrating operant response skill in the offspring of prenatally stressed rats.[38] The research also noted that the offspring of rats showed problems in coping with novelty and spatial learning. Thus, damage to the hippocampus may result in problems with memory and executive function.

In infancy and childhood, overproduction of glucocorticoids and excessive HPA activity appear to adversely impact neurodevelopment, emotional regulation, and intellectual development.[35] Studies highlighting neuropsychological deficits, such as motor problems, poor attention/concentration, poor social/emotional development, decreased balance, and exploratory behaviors, all point to neurodevelopmental problems.[7,39] In addition, maternal stress in the first year of the infant's life, and especially postpartum depression, may increase the vulnerability of the developing child's HPA axis to later stress exposure, and lead to dysregulated behavior.[40]

In animals, the postnatal environment, particularly the quality of maternal care, can alter the expression of genes that regulate responses to stress, in addition to diminishing the development of the hippocampal synapse. Patterns of maternal care that increase infants' stress have significant effects on infants' neural development.[41] In addition, in a study of male boar pups, the way investigators handled the offspring permanently altered HPA function, affecting cortisol level and behavior.[42] Another study in rats found that maternal deprivation (24 hours) caused elevated levels of corticosterone, and the pups continued to show vigorous corticosterone and ACTH responses even to mild stress. In the deprived pups, CRH gene transcription was downregulated, and arginine vasopressin assumed the major regulation of ACTH. Maternal deprivation also caused increased cell death in various regions of the infant brain.[43]

O'Connor et al[44] studied the effects of antenatal anxiety and depression on behavioral and emotional problems in children. In a sample of 7442 mothers, investigators measured maternal depression and anxiety during pregnancy at 18 and 32 weeks and postpartum at 8 and 32 weeks. Maternal depression and anxiety were found to be highly correlated in the antenatal period ($r = 0.72$ and 0.66, $P < .001$) and moderately correlated in the postpartum period ($r = 0.35$ and 0.42, $P < .001$). Findings indicated that significantly elevated anxiety or depression, whether antenatal or postpartum, was associated with a 2 to 3 times increase in the total number of problems in children at 4 years of age. The single most predictive variable for serious behavior problems in children, aged 4 years, was antenatal anxiety at 32 weeks gestation (odds ratio = 1.72, $P = .000$).

In contrast, we postulate that antenatal depression is less a risk and may, in fact, only be a marker of antenatal anxiety. Another study[38] found that human mothers who had high prenatal anxiety in the second trimester of pregnancy also had high depression. Their infants spent more time in deep sleep, and less time in quiet and active alert states, and showed lower motor organization and autonomic stability on the Brazelton Neonatal Behavior Assessment Scale[38] when compared with infants of mothers who did not experience anxiety and depression.

Van der Bergh[45] studied the effects of prenatal maternal stress upon postnatal development of human infants and found that general anxiety in the third trimester of pregnancy was positively correlated with a difficult temperament in infants at 10 weeks and at 7 months postdelivery. General anxiety was not correlated with mental or motor development in infants.[45]

One of the better-controlled human, prenatal stress studies took place at The University Medical Center in Utrecht, Netherlands.[46] The Dutch research team[46] hypothesized that prenatal stress predicted the developmental outcome of human infants. The researchers administered pregnancy-specific stress and anxiety tests and collected salivary cortisol

samples from pregnant women for cortisol determination (an endocrinological index of stress). In addition, researchers administered the Bayley Scales of Infant Development (BSID)[47] and infant temperament questionnaires (dependent measures) at 3 and 8 months. The researchers[46] reported that pregnancy-specific anxiety in midpregnancy predicted lower BSID scores on mental and motor development for infants at 8 months. Overall, the negative effects of mothers' prenatal stress on developmental outcomes of infants were more clear-cut at 8 months than at 3 months. Values of maternal cortisol taken in the early morning during late pregnancy were found to be negatively related to BSID scores on mental and motor development of the infants at 3 months and BSID score on motor development of infants at 8 months.

The effects of pregnancy anxiety in women remained significant after adjusting for possible confounders, such as socioeconomic status, maternal age, birth weight, gestational age, biomedical risks during pregnancy, perinatal complications, and the mothers' postnatal stress and depression levels. The authors[46] indicated that increased maternal stress during pregnancy seems to be one of the determinants of infant temperamental variation and development delays. Levels of perceived stress and maternal ACTH were also associated with problems in the infants' adaptation to a new situation or to the presence of unfamiliar persons. The finding that maternal ACTH was also related to more infant adaptation problems suggests that prenatal stress may adversely affect infant temperament. These findings indicate a strong link of prenatal stress to infants' neurodevelopment. However, there is a gap associating immunity and neurodevelopment as predicted by maternal prenatal stress.

Effects of prenatal stress on thymic function

Over time, it has become clear that the thymus is more than an immune system organ; it is also an endocrine gland.[48] The thymus is the storehouse for immature T lymphocytes and is the primary site from which T lymphocytes differentiate and acquire CD4 or CD8 protein markers and receptors that allow them to bind with specific antigens. Mature T cells are responsible for the majority of specific cellular immune responses. Their major function is to screen the body for all foreign antigens.[49] The prenatal and early postnatal periods are critical for the development of the thymus, and insults during those periods may have more serious consequences in terms of the ability of the T cells to differentiate and mount an appropriate response later in life.[50] The thymus may also be capable of influencing the psychological status of the individual via neurotransmitters.[51] Song[52] indicates that changes in the function of the thymus play an important role in the functional balance among macrophages, cytokines, and lymphocytes, thereby inducing neurotransmitter and neuroendocrine changes, and memory disturbances in depressive illness.

Several animal studies examined the effects of glucocorticoids, given prenatally, on the development of the newborn's immune system. After rats were born, investigators[4] examined the effects of dexamethasone (DEX) on the thymus, spleen, hypothalamus, and blood plasma. DEX exposure resulted in decreased T cell numbers in the thymus and spleen of the newborn rats. Prenatal DEX exposure seemed to delay the migration of T cells into the spleen and exerted major effects on CRH hypothalamic neurons. These facts have implications for enhanced HPA stress responsiveness in later life. Kavelaars et al[53] examined the sensitivity of T cells to DEX in human infants and found that cord blood T cells are extremely sensitive. The DEX-treated T cells inhibited the proliferative response, which did not improve until the infant turned 1 year old. Together, these 2 studies suggest a sensitivity of T cells to cortisol (ie, DEX), indicating a potential long-term effect from HPA dysregulation due to stress.

Evidence indicates that stress affects the thymus. In a study in rats, one group of artificially reared rats was gastrostomized and

reared independently of the mother and another group was reared maternally. Artificially reared rats had lighter thymuses, lower thymic cell numbers, and a greater percentage of necrotic cells than did maternally reared rats.[43] These results have consequences for the development of adult T-cellular immunity. In another study with rhesus monkeys, Hou et al[54] found that juvenile monkeys separated from their social companions overnight had elevated cortisol, increased polymorphonuclear lymphocytes, and fewer CD4 and CD8 (subsets of T cells) lymphocytes when compared with monkeys who were not separated. Von Hertzen[55] hypothesizes that chronic maternal prenatal stress may predispose children to asthma and atopy or allergy prevalence.

The generation of new T cells requires a functional thymus. However, the thymus involutes rapidly after birth. Functionality of the immune system is linked to the receptor diversity of the T-cell pool, as this is how T cells recognize different antigens. Schelonka et al[56] found that the genetic constitution had only a subtle contribution to the immunodeficiency of the newborn and that generation of T-cell diversity is intact by 24 weeks gestation. Neonatal T cells are very sensitive to growth-promoting cytokines, and CD4 and CD8 T cells display distinct response patterns. Therefore, the investigations presented here indicate the potential profound effects of prenatal stress on the functionality of the immune system, particularly the diversity of the T-cell response.

Effects of prenatal stress on infant immune function—cytokines

Many of the research findings concerning the effects of prenatal stress on infant immune responses are from animal models. Coe et al[57] studied rhesus monkeys and found that prenatal chronic stress significantly lowered the cytokine responses in the offspring, lasting up to 2 years after birth. This change in immune response may be due to increased HPA axis activity and consequent high levels of steroids. Using either physiologic (ACTH administration) or psychological prenatal stressors, authors of other studies with rhesus monkeys[58] assessed the potential long-term effects on the cytokine response. The physiologic (ACTH) treatment was found to be the most potent stressor, blunting the IL-1β and IL-6 responses, and diminishing the ability to raise temperature in response to the stressor.

The administration of pro-inflammatory cytokines to human adults induces a pattern of behavioral alterations that appears similar to depression. Pro-inflammatory cytokines appear to influence brain function by affecting serotonergic systems in the brain and peripheral bloodstream. Cytokines also stimulate hypothalamic and preoptic noradrenergic neurotransmission and markedly stimulate the HPA axis. Pro-inflammatory cytokines may thus produce an increased glucocorticoid resistance. Increased levels of cytokines may induce changes in the brain mimicking those found in depressed patients. These findings led to the hypothesis that cytokines induce depression by their influence on the noradrenergic and HPA system.[59]

Several studies indicate the importance of cytokines in relationship to either stress or diseases common in infants. Evidence[60] indicates that IL-10 (anti-inflammatory cytokine) is significantly reduced in intrauterine, growth-retarded placentas. Schultz et al[61] showed that neonates have a poor ability to regulate the responses of anti-inflammatory cytokines during infection. This may predispose infants with immature organ development to harmful effects of pro-inflammatory cytokines. In children, aged 1 to 21 months, an investigation of the cytokine response in respiratory syncytial virus found that both pro-inflammatory and anti-inflammatory cytokines were present. The investigators hypothesized that the balance between the two may dictate the disease outcome in the baby.

A model of the effects of prenatal stress on infant outcomes

Figure 1 summarizes in graphic form the results of the end product of this synthesis

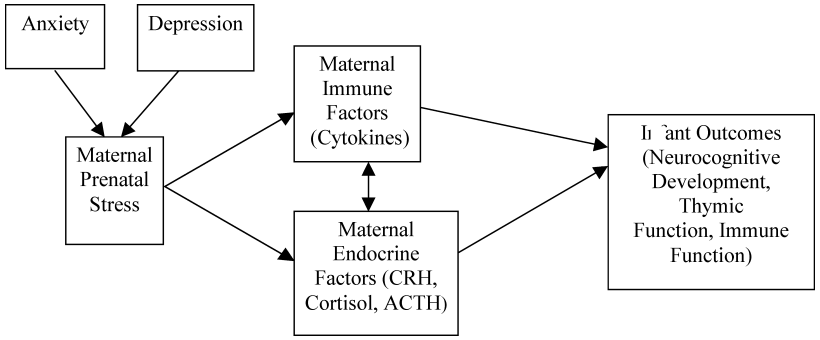

Figure 1. Model of effects of prenatal stress on infant outcomes. CHR indicates corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

of the literature. A pregnant woman's reaction to stress causes an increase in production of CRH, ACTH, and cortisol. Increases in these 3 hormones activate cytokine production in the mother's immune system. A compromised maternal immune system predisposes the mother to infections. Elevated levels of CRH and maternal infection predispose the mother to premature delivery and her infant to problems of prematurity and LBW.

The increase in maternal cytokines downregulates the fetal immune system, including the thymus gland, and may retard the growth of the hippocampus in the fetal brain. The downregulation of the infant immune system may predispose the infant to increased numbers of illnesses in the first year of life. Alterations due to stress may cause a reduction in size of the hippocampus, which in turn may predispose the infant to reduced neurocognitive function and developmental delays.

Implications for nursing practice

Nurses need to be aware of the potentially deleterious effects of prenatal stress on both the mother and her infant. Although studies using human mothers and babies are small in number, evidence is growing that prenatal stress may be hazardous to infant health and well-being. Nurses should screen their prenatal patients for excessive stress. At present, there are few instruments available for measuring prenatal stress. However, nurses can ask simple questions during prenatal visits, and use interview data to assess their patient's stress level. Questions such as "What do you worry most about?" "What is causing you the most stress this week?" "What are you doing to help yourself cope or manage worries and stress?" and "Who is around to help you?" are all good ways to help a patient talk about stress in her life.

Little research is available to support evidence-based interventions for prenatal stress. More research needs to be undertaken on this topic. In the meantime, since stressors may vary significantly among patients, nursing interventions should focus on relieving the particular stress the patient is facing. There are also numerous general stress-reducing interventions, such as relaxation training, yoga, and meditation, that have been used with good effects in nonpregnant patients. From the evidence in this review, the impact of prenatal stress may be significant for the ongoing well-being of the growing child. As effective interventions are refined from research, they may be brought into the clinical setting with the potential to impact the long-term health of the growing child.

Implications for nursing education

The findings from this synthesis can easily be reviewed and taught in graduate classes, such as pathophysiology and reproductive health. Further study is imperative, and including this content in classes will encourage

more students to become interested in the evolution of this vital body of knowledge.

Implications for nursing research and knowledge development

There are several implications for nursing research, not the least of which is the need for sound instruments for measuring acute and chronic stress in pregnancy. At present, there is a paucity of pregnancy-specific tools that can be used for research and/or clinical screening. Short, easy-to-use, reliable, and valid tools would be extremely valuable in the clinical setting in order to focus interventions on the women with the most stress.

More studies need to be undertaken using physiologic measures of stress in addition to psychosocial measures. Very few researchers have attempted to combine measures. More research funding is needed because physiologic studies are very expensive. More convenient access to laboratory facilities is also needed. In addition, the complexity of this type of research requires multidisciplinary teams to provide the expertise needed to plan and conduct such studies. Serious research questions need to be answered. For instance, there is no clear evidence what the threshold is for psychosocial or physical stress needed in a pregnant woman to induce the physiologic arousal initiating the cascade of events reported here. With one or two exceptions, only animal studies provide any evidence of the effect of prenatal stress on infants' immune function. These questions and more need to be explored.

It is not well understood what the physiologic effects of stress are in different ethnic groups of pregnant women. Lower socioeconomic status and poverty create complex confounders of stress. The effects of deprivation with psychosocial stress must be considered when examining different ethnic groups.[62] Multiethnic studies are needed to determine whether stressors affect mothers and babies differently by ethnic group.

Longitudinal studies are also needed to study the effects of prenatal stress on both the mother's immune function and her infant's immune function postnatally. In addition, the interactions between prenatal stress and postnatal stress and how the combined effects may affect the mother and her infant need to be studied.

Finally, studies need to be undertaken on stressor-specific and general stress-reducing techniques as interventions in pregnancy and postpartum. Examples of questions that need to be answered are as follows: Do nursing interventions need to be stressor specific? When is the best time to screen for stress in pregnancy? When is the best time to offer interventions? Do the interventions offered reduce the stress? Do the interventions offered affect the pregnancy outcome or the infant outcomes? and many others.

This is an emerging area of nursing research and much work still needs to be done. But it offers exciting and rewarding opportunities to have a positive impact on the health and well-being of mothers and their infants.

REFERENCES

1. Ruiz RJ, Fullerton J, Brown CEL, Schoolfield J. Relationships of cortisol, perceived stress, genitourinary infections, and fetal fibronectin to gestational age at birth. *Biol Res Nurs*. 2001;3(1):38–48.
2. Ruiz RJ, Fullerton J, Brown CEL, Dudley DJ. Predicting risk of preterm birth: the roles of stress, clinical risk factors, and corticotropin-releasing hormone. *Biol Res Nurs*. 2002;4(1):54–64.
3. Wadhwa PD, Culhane JF, Rauh V, et al. Stress, infection and preterm birth: a biobehavioural perspective. *Paediatr Perinat Epidemiol*. 2001;15(2):17–29.
4. Bakker JM, Schmidt ED, Kroes H, et al. Effects of short-term dexamethasone treatment during pregnancy on the development of the immune system and the hypothalamo-pituitary adrenal axis in the rat. *J Neuroimmunol*. 1995;63(2):183–191.
5. Coe CL, Lubach GR, Karaszewski JW, Ershler W. Prenatal endocrine activation alters postnatal cellular

immunity in infant monkeys. *Brain Behav Immun*. 1996;10(3):221–234.
6. Insel TR, Kinsley CH, Mann PE, Bridges RS. Prenatal stress has long-term effects on brain opiate receptors. *Brain Res*. 1990;511(1):93–97.
7. Schneider ML, Coe CL. Repeated social stress during pregnancy impairs neuromotor development of the primate infant. *J Dev Behav Pediatr*. 1993;14(2):81–87.
8. Schneider ML, Coe CL, Lubach GR. Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the infant primate. *Dev Psychobiol*. 1992;25(6):427–439.
9. Wadhwa PD, Glynn L, Hobel CJ, et al. Behavioral perinatology: biobehavioral processes in human fetal development. *Regul Pept*. 2002;108(2/3):149–157.
10. Ader R, Felten D, Cohen N. Interactions between the brain and the immune system. *Annu Rev Pharmacol Toxicol*. 1990;30:561–602.
11. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis [erratum in *JAMA*. 1992;268(2):200]. *JAMA*. 1992;267(9):1244–1252.
12. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull*. 2004;130(4):601–630.
13. Crump C, Lipsky S, Mueller BA. Adverse birth outcomes among Mexican-Americans: are US-born women at greater risk than Mexico-born women? *Ethn Health*. 1999;4(1/2):29–34.
14. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol*. 2002;21(6):531–541.
15. Herrera JA, Alvarado JP, Martinez JE. The psychosocial environment of the cellular immunity in the pregnant patient. *Stress Med*. 1988;4(1):49–56.
16. Austin MP, Leader L. Maternal stress and obstetric and infant outcomes: epidemiological findings and neuroendocrine mechanisms. *Aust N Z J Obstet Gynaecol*. 2000;40(3):331–337.
17. Zimmer-Gembeck MJ, Helfand M. Low birthweight in a public prenatal care program: behavioral and psychosocial risk factors and psychosocial intervention. *Soc Sci Med*. 1996;43(2):187–197.
18. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *Am J Obstet Gynecol*. 1993;169(4):858–865.
19. McCool WF, Dorn LD, Susman EJ. The relation of cortisol reactivity and anxiety to perinatal outcome in primiparous adolescents. *Res Nurs Health*. 1994;17(6):411–420.
20. Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. *Health Psychol*. 1992;11(1):32–40.
21. Lobel M, Dunkel-Schetter C. Conceptualizing stress to study effects on health: environmental, perceptual, and emotional components. *Anxiety Res*. 1990;3:213–230.
22. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychol*. 1999;18(4):333–345.
23. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. *Health Psychol*. 2000;19(6):535–543.
24. Susman EJ, Schmeelk KH, Worrall BK, Granger DA, Ponirakis A, Chrousos GP. Corticotropin-releasing hormone and cortisol: longitudinal associations with depression and antisocial behavior in pregnant adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38(4):460–467.
25. Schmeelk KH, Granger DA, Susman EJ, Chrousos GP. Maternal depression and risk for postpartum complications: role of prenatal corticotropin-releasing hormone and interleukin-1 receptor antagonist. *Behav Med*. 1999;25(2):88–94.
26. Ruggiero DA, Underwood MD, Rice PM, Mann JJ, Arango V. Corticotropic-releasing hormone and serotonin interact in the human brainstem: behavioral implications. *Neuroscience*. 1999;91(4):1343–1354.
27. Petraglia F, Florio P, Nappi C, Genazzani AR. Peptide signaling in human placenta and membranes: autocrine, paracrine, and endocrine mechanisms. *Endocr Rev*. 1996;17(2):156–186.
28. Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. *Psychosom Med*. 1996;58(5):432–446.
29. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response: the 1997 Hans Selye Memorial Lecture. *Ann N Y Acad Sci*. 1998;851:311–335.
30. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann N Y Acad Sci*. 2002;966:290–303.
31. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci*. 2004;1024:138–146.
32. Daher S, de Arruda Geraldes Denardi K, Blotta MH, et al. Cytokines in recurrent pregnancy loss. *J Reprod Immunol*. 2004;62(1–2):151–157.
33. Dame JB, Juul SE. The distribution of receptors for the pro-inflammatory cytokines interleukin (IL)-6 and IL-8 in the developing human fetus. *Early Hum Dev*. 2000;58(1):25–39.
34. Francis D, Diorio J, LaPlante P, Weaver S, Seckl JR, Meaney MJ. The role of early environmental events in regulating neuroendocrine development. Moms,

pups, stress, and glucocorticoid receptors. *Ann N Y Acad Sci*. 1996;794:136–152.
35. Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: potential effects on the developing human brain. *Prev Med*. 1998;27(2):208–211.
36. Goldstein S, Reynolds CR. *Handbook of Neurodevelopmental and Genetic Disorders in Children*. New York: Guilford Press; 1999:602.
37. Lezak MD. *Neuropsychological Assessment*. 3rd ed. New York: Oxford University Press; 1995.
38. Smith BL, Wills G, Naylor D. The effects of prenatal stress on rat offsprings' learning ability. *J Psychol*. 1981;107(1st Half):45–51.
39. Schneider ML. Delayed object permanence development in prenatally stressed rhesus monkey infants (*Macaca mulatta*). *Occup Ther J Res*. 1992;12:96–110.
40. Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biol Psychiatry*. 2002;52(8):776–784.
41. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci*. 2001;24:1161–1192.
42. Weaver SA, Aheme FX, Meaney MJ, Schaefer AL, Dixon WT. Neonatal handling permanently alters hypothalamic-pituitary-adrenal axis function, behaviour, and body weight in boars. *J Endocrinol*. 2000;164(3):349–359.
43. Levine S. Regulation of the hypothalamic-pituitary-adrenal axis in the neonatal rat: the role of maternal behavior. *Neurotoxic Res*. 2002;4(5/6):557–564.
44. O'Connor TG, Heron J, Glover V, Alspac Study Team. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1470–1477.
45. Van den Bergh B. Maternal emotions during pregnancy and fetal and neonatal behaviour. In: Nijhuis JG, ed. *Fetal Behaviour: Developmental and Perinatal Aspects*. Oxford: Oxford University Press; 1992;157–178.
46. Buitelaar JK, Huizink AC, Mulder EJ, de Medina PG, Visser GH. Prenatal stress and cognitive development and temperament in infants. *Neurobiol Aging*. 2003;24(suppl 1):S53–S60.
47. Bayley N. *Bayley Scales of Infant Development*. San Antonio, Tex: Psychological Corp; 1993.
48. Ader R, Felten D, Cohen N. *Psychoneuroimmunology*. 2nd ed. New York: Academic Press; 1991.
49. Sigal LH, Ron Y. *Immunology and Inflammation: Basic Mechanisms and Clinical Consequences*. New York: Health Professions Divisions, McGraw-Hill; 1994:805.
50. McDade TW, Beck MA, Kuzawa CW, Adair LS. Prenatal undernutrition and postnatal growth are associated with adolescent thymic function. *J Nutr*. 2001;131(4):1225–1231.
51. Hall NR, McGillis JP, Spangelo BL, Goldstein AL. Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. *J Immunol*. 1985;135(2, suppl):806s–811s.
52. Song C. The effect of thymectomy and IL-1 on memory: implications for the relationship between immunity and depression. *Brain Behav Immun*. 2002;16(5):557–568.
53. Kavelaars A, Cats B, Visser GH, et al. Ontogency of the responses of human peripheral blood T cells to glucocorticoids. *Brain Behav Immun*. 1996;10(3):288–297.
54. Hou FY, Coe CL, Erickson C. Psychological disturbance differentially alters CD4+ and CD8+ leukocytes in the blood and intrathecal compartments. *J Neuroimmunol*. 1996;68(1/2):13–18.
55. von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J Allergy Clin Immunol*. 2002;109(6):923–928.
56. Schelonka RL, Raaphorst FM, Infante D, Kraig E, Teale JM, Infante AJ. T cell receptor repertoire diversity and clonal expansion in human neonates. *Pediatr Res*. 1998; 43(3):396–402.
57. Coe CL, Kramer M, Kirschbaum C, Netter P, Fuchs E. Prenatal stress diminishes the cytokine response of leukocytes to endotoxin stimulation in juvenile rhesus monkeys. *J Clin Endocrinol Metab*. 2002;87(2):675–681.
58. Reyes TM, Coe CL. Prenatal manipulations reduce the proinflammatory response to a cytokine challenge in juvenile monkeys. *Brain Res*. 1997;769(1):29–35.
59. Wichers M, Maes M. The psychoneuroimmunopathophysiology of cytokine-induced depression in humans. *Int J Neuropsychopharmacol*. 2002;5(4):375–388.
60. Hahn-Zoric M, Hagberg H, Kjellmer I, Ellis J, Wennergren M, Hanson LA. Aberrations in placental cytokine mRNA related to intrauterine growth retardation. *Pediatr Res*. 2002;51(2):201–206.
61. Schultz C, Temming P, Bucsky P, Gopel W, Strunk T, Hartel C. Immature anti-inflammatory response in neonates. *Clin Exp Immunol*. 2004;135(1):130–136.
62. Pike I. Maternal stress and fetal responses: evolutionary perspectives on preterm delivery. *Am J Human Biol,* 2004;17:55–65.