Stress, infection and preterm birth: a biobehavioural perspective

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Summary
Preterm birth is currently the most important problem in maternal-child health in the United States. Epidemiological studies have suggested that two factors, maternal stress and maternal urogenital tract infection, are significantly and independently associated with an increased risk of spontaneous preterm birth. These factors are also more prevalent in the population of sociodemographically disadvantaged women who are at increased risk for preterm birth. Studies of the physiology of parturition suggest that neuroendocrine and immune processes play important roles in the physiology and pathophysiology of normal and preterm parturition. However, not all women with high levels of stress and/or infection deliver preterm, and little is understood about factors that modulate susceptibility to pathophysiological events of the endocrine and immune systems in pregnancy. We present here a comprehensive, biobehavioural model of maternal stress and spontaneous preterm delivery. According to this model, chronic maternal stress is a significant and independent risk factor for preterm birth. The effects of maternal stress on preterm birth may be mediated through biological and/or behavioural mechanisms. We propose that maternal stress may act via one or both of two physiological pathways: (a) a neuroendocrine pathway, wherein maternal stress may ultimately result in premature and/or greater degree of activation of the maternal-placental-fetal endocrine systems that promote parturition; and (b) an immune/inflammatory pathway, wherein maternal stress may modulate characteristics of systemic and local (placental-decidual) immunity to increase susceptibility to intrauterine and fetal infectious-inflammatory processes and thereby promote parturition through pro-inflammatory mechanisms. We suggest that placental corticotropin-releasing hormone may play a key role in orchestrating the effects of endocrine and inflammatory/immune processes on preterm birth. Moreover, because neuroendocrine and immune processes extensively cross-regulate one another, we further posit that exposure to both high levels of chronic stress and infectious pathogens in pregnancy may produce an interaction and multiplicative effect in terms of their combined risk for preterm birth. Finally, we hypothesise that the effects of maternal stress are modulated by the nature, duration and timing of occurrence of stress during gestation. A discussion of the components of this model, including a theoretical rationale and review of the available empirical evidence, is presented. A major strength of this biobehavioural perspective is the ability to explore new questions and to do so in a manner that is more comprehensive than has been previously attempted. We expect findings from this line of proposed research to improve our present state of knowledge about obstetric risk assessment for preterm birth by determining the characteristics of pregnant women who are especially susceptible to stress and/or infection, and to broaden our understanding of biological (endocrine, immune, and endocrine-immune interactions) mechanisms that may translate social adversity during pregnancy into pathophysiology, thereby suggesting intervention strategies.

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Introduction

Preterm birth is currently the most significant problem in maternal-child health in the United States because it is associated with severe adverse health consequences, it has a relatively high prevalence rate that has remained essentially unchanged over the past four decades, and the aetiology is poorly understood. Current approaches to obstetric risk identification for preterm birth involve the consideration of biomedical (obstetric), sociodemographic and behavioural factors at the individual and/or population level. The major limitations of this approach are, first, that currently identified risk factors have accounted for only about one-half of all preterm births; second, that their sensitivity and specificity is, at best, only modest, even when the major subtypes of preterm birth (i.e. medically indicated preterm births and spontaneous preterm births preceded by preterm labour or preterm rupture of membranes) are considered separately; and third, that many of these established risk factors do little to further an understanding of the aetiology of preterm birth because they are not causal in nature but instead probably represent markers of more proximate, underlying causal processes (e.g. history of prior preterm birth, African-American race/ethnicity, low socio-economic status). Thus, it is not surprising that although several risk-scoring systems for predicting preterm birth have been constructed, they have yielded little success, and no current intervention or practice has produced an appreciable impact on the prevention or reduction of preterm birth in the US. Although much has been learned from the study of discrete risk factors, this approach has led to a rather limited view of perinatal risk assessment because individual risk factors tend to co-occur, leading to apparent interactive effects, and because individual risk factors also often yield different predictive power in different populations.

While it is not only possible but very probable that future research will uncover new factors involved in the aetiology of preterm birth, it is also clear that much progress remains to be made in developing a more comprehensive approach that incorporates and synthesises the state of present knowledge from clinical obstetrics, developmental biology, endocrinology, immunology, genetics, epidemiology and the behavioural sciences into a more cohesive and parsimonious understanding of the role(s), and interplay between, various individual risk factors. To yield maximal dividends, such a comprehensive approach must necessarily incorporate an appreciation and understanding of the heterogeneity of preterm birth, the physiological processes involved in parturition (including the temporal course and sequence of events associated with gestation and parturition), and processes associated with heightened individual vulnerability to the effects of various risk factors. This, in our view, calls for the adoption of a biobehavioural systems perspective to address the problem of preterm birth.

Prenatal stress as a central, organising biobehavioural construct

Prenatal stress is perhaps a common theme that runs across many individual as well as group-level sets of risk factors for preterm birth. We argue here that the construct of prenatal stress and stress biology may serve as a useful, central organising concept to develop an integrative biobehavioural framework to understand better the interplay across, and vulnerability to, a range of established discrete risk factors for preterm birth for the reasons outlined below.

- First, the developmental neurosciences strongly support an epigenetic model of development, wherein the prenatal environment plays a necessary and crucial role in interacting with the genome to shape all aspects of development. Environment, or experience, is a double-edged sword, wherein optimal environments produce beneficial effects, and hostile environments, such as those affected by stress, produce deleterious effects on the developing brain and other organ systems.

- Second, a large number of epidemiological studies support a role for maternal psychosocial stress, which is a significant and independent risk factor for preterm birth.

- Third, studies that have investigated the causes of the wide disparity in preterm birth rates between sociodemographically advantaged and disadvantaged women (i.e. by age, marital status, income, education, occupation) have found that behavioural factors such as prenatal health-care availability and utilisation patterns, and practices related to diet, nutrition, physical activity, and high-risk health behaviours such as smoking, alcohol/drug use, play only a limited role in accounting for the magnitude of this disparity. Prenatal stress remains a viable alternative explanation here, in part because of the strong observed association between conditions of social disadvantage and the experience of social and physiological stress.
Fourth, an almost two-fold disparity persists in the incidence of preterm birth between African-American women and non-Hispanic white women in the US today, even after accounting for the effects of the sociodemographic, access-to-care and behavioural factors.\textsuperscript{22-24} This has led to the suggestion that these racial/ethnic discrepancies may be accounted for by genetic differences between these groups. This, however, is also an unlikely explanation for at least two reasons. Although much remains to be understood in terms of the specific genetics of embryonic/fetal development and parturition, broader investigations of genetic differences along racial/ethnic characteristics suggest, in fact, far greater genetic variability within racial/ethnic populations (approximately 85%) and relatively smaller systematic differences across populations (approximately between 6 and 9%).\textsuperscript{25-28} Moreover, there are consistent findings from the acculturation literature that demonstrate that within racial/ethnic minority immigrant populations in the United States there is a rapid increase in the incidence of adverse health outcomes, including preterm birth, that is positively associated with the duration of stay in the US and is not accounted for by socio-economic and lifestyle variables.\textsuperscript{22,29-32} These findings argue against the possibility of systematic genetic differences along racial/ethnic lines in the causation of this phenomenon. Again, prenatal stress remains a plausible candidate as a potential mediator of the effects of race/ethnicity on preterm birth.

Fifth, results from animal studies demonstrating the intergenerational transmission of environmental effects by non-genomic mechanisms\textsuperscript{33} provide important clues that point to the possible role of pre- and perinatal stress and stress biology in mediating the effects of adverse environments not only on the individuals experiencing such conditions during gestation, but also in terms of the transduction of increased vulnerability for adverse gestational outcomes to subsequent generations.

Sixth, at the individual level, maternal-placental-fetal neuroendocrine pathophysiology (of largely unknown origin) and maternal-placental-fetal infections and related immune pathophysiology are presently among the leading candidates for further investigation of causal biological processes that underlie spontaneous preterm birth. Maternal (prenatal) stress is, yet again, a plausible factor in producing and/or increasing individual vulnerability for endocrine and/or immune pathophysiology during gestation, as discussed below.

**Maternal stress and preterm birth**

A growing body of empirical evidence, based on prospective, relatively methodologically rigorous, population-based studies in pregnant women of different ethnic, socio-economic, and national backgrounds, now provides substantial support for the premise that women experiencing high levels of psychological or social stress during pregnancy are at significantly increased risk for shorter gestation, earlier onset of spontaneous labour, and preterm delivery, even after adjusting for the effects of other established biomedical, sociodemographic, and behavioural risk factors.\textsuperscript{19,34-46} In fact, several reviews of the role of psychosocial factors in pregnancy outcomes have concluded that the relationship between high prenatal stress and shorter gestation is among the more consistent and unambiguous set of findings in this area.\textsuperscript{46}

However, it is clear that not all women reporting high levels of psychosocial stress deliver preterm, and several important questions remain about vulnerability to stress in pregnancy. These questions include issues about the nature of stressful experience (including issues related to the assessment of individual as well as community levels of stress), the timing of occurrence of stress before and/or during gestation, the nature of the combined effects of stress and other obstetric risk factors such as infection on adverse outcomes, and the elucidation of the biological and/or behavioural mechanisms that mediate the effects of stress on gestational outcomes.

**Infection and preterm birth**

Microbial colonisation and inflammation in the maternal genital tract has emerged as one of the major risk factors associated with spontaneous preterm birth. Bacterial vaginosis (BV) is the most common lower genital tract infection in women of reproductive age. This condition, often considered a clinical syndrome, is characterised by an alteration of the normal vaginal flora rather than an infection specific to any one micro-organism, and is associated with a reduced concentration of normally abundant lactobacilli along with high concentrations of Gram-negative and anaerobic bacteria.\textsuperscript{47,48} The prevalence of BV in human pregnancy is estimated to range between 15 and 40%, with
significantly higher rates among sociodemographically disadvantaged women, including African-American, poor, unmarried, less-educated and younger women. Little is known about the mediating mechanisms between sociocultural factors and bacterial infections in pregnancy. Although behavioural practices such as number of lifetime sexual partners and douching are associated with higher-than-expected rates of BV infection, they account for only a small proportion of the sociodemographic disparity in the BV prevalence rate.

The presence of BV in pregnancy is associated with an approximately twofold increase in the risk of preterm labour and premature rupture of membranes. This relationship between infection and preterm delivery is not consistent throughout gestation. Infection (chorioamnionitis) is present in the vast majority of early preterm births (i.e. < 28 weeks' gestation) but is infrequently present in later preterm births (i.e. 34–36 weeks' gestation). Several issues remain unanswered about the role of infection in preterm birth, including issues related to the pathogenicity of specific infectious organisms, the timing of infection during gestation, the site(s) of infection/inflammation, and pathophysiological mechanisms that mediate the effects of infection. An issue of particular interest in the present context concerns individual susceptibility to infection. Two questions emerge. First, what is/are the factor(s) that modulate susceptibility to developing BV during pregnancy? Second, based on the findings that not all women with BV during pregnancy deliver prematurely, what are the factors that modulate susceptibility to preterm birth in the presence of BV?

**Stress physiology: a brief overview**

The term stress is used to describe any physical or psychological challenge that threatens or is perceived to have the potential to threaten the stability of the internal milieu of the organism (homeostasis). The neuroendocrine and immune systems play a major role in adaptation to stress. The principal effectors of these adaptive responses are the corticotropin-releasing hormone (CRH) and locus ceruleus-noradrenaline (LC/NA)/autonomic (sympathetic) neurons in the hypothalamus and brain stem, which regulate the peripheral activities of the hypothalamic-pituitary-adrenal (HPA) axis and the systemic/adrenomedullary sympathetic nervous system, respectively. Activation of the HPA axis and LC-NA/autonomic system results in the systemic elevation of glucocorticoids and catecholamines, respectively, which act in concert to maintain or effect a return to the state of homeostasis. Any immune challenge that threatens homeostasis can be regarded as a stressor. Certain cytokines, especially tumour necrosis factor-alpha (TNF-α), interleukin 1 (IL-1) and IL-6 activate the stress system in vivo. Stress that is associated with an immune challenge has been called immune or inflammatory stress and, as with 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 (IFN-γ), led to the initial conclusion that stress was, in general, immunosuppressive. Recent evidence, however, suggests that stress-induced concentrations of glucocorticoids and catecholamines may influence the immune response in a less monochromatic way. Immune responses are regulated by antigen-presenting cells such as monocytes and macrophages, which are components of innate immunity, and by 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. Naïve CD4+ (antigen-inexperienced) Th0 cells are bipotential and 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 currently known to influence differentiation of Th0 cells towards the Th1 or Th2 subsets to drive cellular and humoral immune responses. Th1 and Th2 responses are mutually inhibitory. Evidence over the past few years strongly suggests that stress hormones differentially regulate Th1/Th2 patterns and type1/type2 cytokine secretion, thereby potentially altering the balance between these two arms of acquired immune responses.

**A biobehavioural model of stress, infection and preterm birth**

Based on the evidence linking maternal stress and infection to preterm birth and on an understanding of the physiology of stress and parturition, we present here a biobehavioural model of stress and preterm delivery. This model proposes that chronic maternal stress is a significant and independent risk factor for
preterm birth. The effects of maternal stress on preterm birth may be mediated through biological and/or behavioural mechanisms. Maternal stress may act via one or more of two major physiological pathways: (a) a neuroendocrine pathway to ultimately result in premature and/or greater degree of activation of the maternal-placental-fetal endocrine systems that promote parturition; and (b) an immune/inflammatory pathway wherein maternal stress may modulate characteristics of systemic and local (placental-decidual) immunity to increase susceptibility to intrauterine and fetal infectious-inflammatory processes and thereby promote parturition through pro-inflammatory mechanisms. Moreover, because neuroendocrine and immune processes extensively cross-regulate one another, we posit that exposure to both high levels of chronic stress and infectious pathogens in pregnancy produces an interaction and multiplicative effect in terms of their combined risk for preterm birth. We further suggest that placental CRH plays a key role in co-ordinating the effects of endocrine, inflammatory/immune and vascular processes on preterm birth. Finally, we hypothesise that the effects of maternal stress are modulated by the nature, duration and timing of occurrence of stress during gestation. The various components of this model are discussed below.

The pathophysiology of stress in parturition

Parturition is the process involving changes in gestational tissues (i.e. uterus, cervix, and membranes) that result in birth, as well as the events in the maternal, placental and fetal compartments that lead to these changes (i.e. myometrial activation and stimulation, and enhanced genital tract protease activity promoting the rupture of membranes and cervical changes). The precise biomolecular mechanisms by which human parturition is initiated spontaneously, either at term or preterm, are not well understood. However, several processes or pathways involved in various facets of parturition have been identified, including endocrine and immune/inflammatory actions on the mother and/or fetus, and autocrine or paracrine actions within the placenta, decidua and myometrium.64

Neuroendocrine processes in parturition

Within the pregnant uterus, starting at 7–9 weeks gestation, the fetal-placental-decidual unit produces hormones, neuropeptides, growth factors, and cytokines, and appears to function in a manner resembling that of compressed hypothalamic-pituitary-target systems. Pregnancy is associated with major alterations in neuroendocrine function, including changes in hormone levels and control mechanisms (feedback loops), that are crucial in providing a favourable environment within the uterus for cellular growth and maturation and conveying signals when the fetus is ready for extrauterine existence.65 It is now well-recognised that a shift in the balance from a progesterone-dominant to an oestrogen-dominant milieu results in a sequence of events in the gestational tissues to promote labour, including gap junction formation, expression of oxytocin receptors, and synthesis of prostaglandins. It is also known that unlike most other mammals, the human (primate) placenta cannot convert progesterone to oestrogen because it does not express the cortisol-responsive enzyme 17-hydroxylase required for this conversion. Instead, the fetal adrenal zone produces a precursor hormone – dehydroepiandrosterone sulphate (DHEA-S) – that is used by the placenta to synthesise oestrogens.66

CRH is a hypothalamic neuropeptide that plays a central role in regulating the activity of the HPA axis and physiological response to stress.67,68 During human pregnancy the CRH gene is also expressed in the placenta and membranes, and results in the exponentially increasing production and release of placental CRH into both maternal and fetal compartments over the course of gestation.69,70 A growing body of empirical evidence supports a central role for placental CRH in orchestrating and coordinating fetal and maternal endocrine events involved in parturition. For example, placental CRH has recently been shown to directly and preferentially stimulate DHEA-S secretion by human fetal adrenal cortical cells.71 Placental CRH is also known to exert direct actions on the uterus and cervix to augment changes produced by oestrogens on these tissues. CRH interacts with both prostaglandins and oxytocin, the two major uterotonin implicated as mediators of the stimulation and maintenance of myometrial contractility at term and during labour, by stimulating the release of prostaglandins from the placenta and fetal membranes72,73 and exerting priming as well as potentiating effects for the actions of oxytocin on the myometrium.74,75

The overwhelming evidence from clinical studies that have examined the association between maternal
plasma concentrations of CRH and spontaneous preterm labour/birth suggests that women in preterm labour have significantly elevated levels of CRH compared with gestational age-matched controls, and that these elevations of CRH precede the onset of preterm labour, in some instances by several weeks.\textsuperscript{76-84} Two studies that conducted serial assessments of CRH over the course of gestation found that when compared with term deliveries, women delivering preterm had not only significantly elevated CRH levels but also a significantly accelerated rate of CRH increase over the course of their gestation.\textsuperscript{77,85} Moreover, we have shown that the effects of placental CRH on spontaneous preterm birth are independent from those of other biomedical risk factors.\textsuperscript{82}

Placental CRH is stress-sensitive. A series of \textit{in vitro} studies by Petraglia and colleagues\textsuperscript{85-87} have shown that CRH is released from cultured human placental cells in a dose-response manner in response to all the major biological effectors of stress, including cortisol, catecholamines, oxytocin, angiotensin-II, and both forms of interleukin-1. \textit{In vivo} studies by our group\textsuperscript{98} and other investigators\textsuperscript{88-91} have found significant correlations among maternal pituitary-adrenal stress hormones (ACTH, cortisol) and placental CRH levels. The maternal environment may also modulate placental CRH via its influence on maternal pituitary-adrenal function. We have reported significant associations between maternal psychosocial stress and two effectors of placental CRH – maternal ACTH and cortisol – in the early third trimester of gestation.\textsuperscript{92} In addition, a recent study by Hobel \textit{et al.}\textsuperscript{77} reported that maternal psychosocial stress levels at mid-gestation significantly predicted the magnitude of increase in maternal CRH levels between mid-gestation and later gestation. Thus, depending on the chronicity of the stressor, the resultant increase in CRH production may be a critical factor that contributes to the early initiation of spontaneous labour.\textsuperscript{69-93}

\textbf{Immune/inflammatory processes in parturition}

As reviewed earlier, microbial infection and inflammation in the gestational tissues has emerged as one of the major risk factors associated with spontaneous preterm birth. Preterm labour and/or premature rupture of membranes in the setting of infection is believed to result from the actions of pro-inflammatory cytokines secreted as part of the fetal and/or maternal host response to microbial invasion.\textsuperscript{94,95} Maternal infections may trigger parturition by the activation of the monocyte and macrophage system in peripheral blood and human decidua, resulting in release of inflammatory cytokines in some, but not all, cases. Such inflammatory cytokines have been detected in elevated concentrations in the amniotic fluid and plasma of women with preterm labour/premature rupture of membranes, and human gestational tissues are potentially rich sources of inflammatory cytokines. Also, maternal decidua and fetal membranes produce mRNA for inflammatory cytokines in the setting of infection-associated preterm labour and normal term labour. Animal models indicate that preterm labour can be stimulated by bacteria, bacterial cell-wall products, and pro-inflammatory cytokines such as IL-1 and tumour necrosis factor.\textsuperscript{1} There is strong evidence that prostaglandins E2 and F2\alpha (PGE2 and PGF2\alpha) are involved in the initiation and maintenance of human parturition, and that their production can be stimulated by a number of cytokines and in infection-induced preterm labour by bacterial endotoxin.\textsuperscript{96} Romero and colleagues have argued that infection-related preterm labour and preterm premature rupture of membranes are expressions of the same basic phenomenon: activation of the host-defence macrophage system. Intrauterine infection causes preterm labour in some cases if the preferential response of the host favours secretion of uterotonic agents (i.e. prostaglandins), and preterm rupture of membranes if the host response results predominantly in the production of proteases. A growing body of recent work also suggests a systemic fetal proinflammatory cytokine response, accompanied by activation of the fetal HPA axis, precedes the onset of spontaneous parturition.\textsuperscript{94,97,98}

Normal pregnancy is an immunological balancing act, wherein alterations are produced in the maternal immune system to tolerate paternal major histocompatibility (MHC) antigens (the embryo and fetus is a semiallograft for the mother because it shares one-half of its genomic complement with the father) and yet also to maintain adequate immune competence for defence against micro-organisms. The mechanisms underlying this process are complex and not yet completely clarified, but are known to involve systemic as well as local changes at the maternal-placental-fetal interface.\textsuperscript{99} It has long been recognised that, over the course of gestation, lymphocytes from pregnant women exhibit a progressive decline in their ability to proliferate in response to mitogenic
stimuli\textsuperscript{100,101} – a hallmark of general immunosuppression. More recent studies indicate that in addition to a decreased proliferative response there is a change in the normal pattern of cytokine production from a T-helper cell (Th)-1 (favouring cellular immunity) to a Th2 (favouring humoral immunity) cytokine profile in pregnancy.\textsuperscript{102} Recent findings suggest that normal full-term delivery is associated with a predominance of Th2 cytokine production, whereas spontaneous abortion or preterm delivery is associated with the maintenance of a Th1 cytokine profile.\textsuperscript{103-106}

Although a number of studies have postulated that incomplete shifting from a Th1 to Th2 cytokine profile is a key factor in both spontaneous abortions and preterm delivery, other investigators have proposed that enhanced expression of the proinflammatory cytokines IL-1, IL-6 and TNF-\(\alpha\) are associated with preterm delivery.\textsuperscript{106,107} IL-1 is also highly associated with the presence of BV.\textsuperscript{108} The pro-inflammatory cytokines can be induced by a number of stimuli, including bacterial endotoxins. However, the Th1 cytokines, particularly INF-\(\gamma\), can also induce monocytes and endothelial cells to produce these proinflammatory cytokines. Thus, it is unclear whether the increased pro-inflammatory cytokines associated with preterm delivery represent a direct response to bacterial endotoxins or an induction by Th1 cells that were ineffectively downregulated.

Proinflammatory cytokines, endotoxins and exotoxins have been shown to promote spontaneous labour and rupture of membranes via their actions in the gestational tissues to stimulate the synthesis and release of prostaglandins and metalloproteinases, respectively, and in the fetus and placenta to stimulate fetal cortisol and DHEA-S and placental CRH synthesis and release.\textsuperscript{86,87,94,109} Moreover, a recent in vivo study reported that subjects in preterm labour with microbial invasion of the amniotic cavity had significantly higher CRH levels than those in preterm labour without infection.\textsuperscript{81}

Although this growing body of empirical evidence suggests that chronic stress and stress hormones are associated with immunosuppression and changes in the normal pattern of cellular (Th1) and humoral (Th2) responses to antigens,\textsuperscript{63} and although maternal stress and infection have been implicated as risk factors in preterm birth, the nature of the stress-immune-infection relationship has not been studied in human pregnancy to date. In fact, our review of the relevant literature found only one study of stress and immunity in human pregnancy. In cross-sectional investigation in a sample of 72 pregnant women, Herrera et al.\textsuperscript{110} reported that high levels of maternal psychological stress and low levels of social support were significantly associated with depression of lymphocyte activity.

**Neural-endocrine-immune interactions**

Stress-induced changes in immune responses are believed to be produced via physiological mechanisms involving the autonomic nervous system and the HPA axis. As reviewed earlier, it is now well-established that the neuroendocrine system is an important modulator of immune function. Under conditions of chronic stress, moderate to high levels of glucocorticoids (e.g. cortisol) exert several direct effects on the immune system. These include inhibiting the production and response of lymphocytes to pro-inflammatory cytokines, suppressing the expression of proenkaphalin mRNA, suppressing the differentiation of T-cells, early events in B-cell activation, and monocyte to macrophage differentiation, and inhibiting the expression of MHC-I.\textsuperscript{111,112} The tissues and organs of the immune system are innervated by the autonomic nervous system and contain receptors for several endocrine and paracrine hormones. Cortisol also exerts indirect effects on the immune system by modulating the expression of the parasympathetic and sympathetic components of the nervous system on thymocytes, monocytes and macrophages.\textsuperscript{62,112} These effects are believed to be mediated by a large infrastructure of anatomical and physiological connections that allow communication both within and between the endocrine and immune systems. For example, the efferent sympathetic-adrenomedullary system participates in the interactions of the HPA axis and immune/inflammatory stress by being reciprocally connected with the CRH system, by transmitting humoral and nervous signals to lymphoid organs, and by reaching sites of inflammation via postganglionic sympathetic neurons.\textsuperscript{62} Immune cells contain receptors for and respond to neurotransmitters, neuropeptides and neurohormones secreted by sympathetic neurons and/or the adrenal medulla. This combination of cortisol and catecholamines during stress thus results in a transient shift from cellular to humoral immune response predominance, which is adaptive in an acute situation but maladaptive in a chronic situation (perhaps including pregnancy) because it
results in increased vulnerability to infectious agents that are defended against primarily via cellular immune responses.62

The importance of understanding these linkages in pregnancy between stress and infection on the one hand, and the endocrine and immune systems on the other hand, has been further underlined by the work of Roberto Romero and his colleagues. They described a condition that they termed ‘Fetal Inflammatory Response Syndrome (FIRS)’, that is characterised by a multisystem fetal stress response in human pregnancy, with activation of haemostatic, endocrine and immune systems that result in outpouring of matrix-degrading enzymes into fetal circulation,113 elevated fetal cortisol/DHEA-S ratio,114 and elevated levels of inflammatory cytokines in fetal circulation114,115 – all of which are important biochemical mediators of spontaneous preterm premature rupture of membranes and onset of preterm labour.94

Research issues and future directions

Clearly, parturition is a complex and dynamic process involving the participation of, and interplay between, multiple fetal and maternal systems. Although much work still remains to be done to arrive at a clearer understanding of the processes involved in parturition, we hope the state of the current literature and our discussions presented above support our argument that the adoption of an integrated, biobehavioural perspective may yield dividends in our examination of the problem of preterm birth. There is considerable heterogeneity in terms of the distribution of preterm birth across and within populations as well as variability in terms of individual susceptibility in the presence of risk factors. We have used the construct of prenatal stress as an organising theme in our discussion of a biobehavioural approach because it affords a plausible and parsimonious explanation for this heterogeneity and variability at both the social and biological levels of analysis.

There is a need for subsequent research on the determinants and consequences of maternal stress in human pregnancy in order to address several issues, including questions about stressor-specificity, outcome-specificity, and the timing of stress during gestation. Although there is no universally accepted definition of stress, it is clear that stress is not a unidimensional construct, but rather ‘a person–environment interaction’, in which there is a perceived discrepancy between environmental demands and the individual’s biological, psychological or social resources.116 This transactional view of the stress construct calls for the identification of stressful stimuli, subjects’ appraisal of these stimuli, and their response, especially emotional response. Moreover, stress may not entirely be an individual-level phenomenon, but may also be linked to the individual’s social-structural context.117,118

The construct of prenatal stress and the social-structural context within which stress is experienced by the individual are clearly areas that need further refinement in our effort to understand better the role(s) of prenatal stress in preterm birth. Preterm birth is a heterogenous entity in terms of the extent to which the birth is preterm (mild, moderate, or severe), as well as in terms of the precipitating events (elective preterm birth or spontaneous preterm birth following either preterm labour or preterm rupture of membranes). It is important to recognise and examine the possibility that various categories within preterm birth may be differentially linked to maternal stress.

It is well-established that there are several sensitive or critical periods in development,119 and there may be critical periods during pregnancy when the determinants of parturition are especially vulnerable to the effects of prenatal stress. These periods may be related to the times in gestation corresponding to specific developmental events (e.g. maturation of the fetal HPA axis), and/or to time-specific changes in maternal or fetal physiological responses to stress over the course of gestation. Although this premise of susceptible periods is well-supported in the animal literature, few human studies of prenatal stress have incorporated multiple assessments of stress over the course of gestation, and even fewer studies have tested hypotheses about time-specific effects of prenatal stress. We and others have shown, for example, that maternal psychological as well as physiological responses to exogenous stimuli such as stress are progressively attenuated as gestation advances, with important implications for the timing of occurrence of stress in terms of its impact on the length of gestation.18,19

Pregnancy produces significant alterations in physiological systems, including the systems (i.e. endocrine and immune) that participate in parturition. Moreover, pregnancy-induced alterations are dynamic and progressive over the course of gestation. For these reasons it may be important to obtain serial assessments of appropriate physiological parameters to characterise the trajectory of these systems over the
course of gestation, rather than use single measurements at any given point in time, to arrive at a more dynamic and therefore better understanding of the determinants and consequences of these alterations on parturition and preterm birth. The collection of naturalistic psychological and biological stress-related data over the course of gestation permits some degree of quantification of the ‘load’ placed upon the individual (e.g. the concept of allostatic load) but does little to quantify individual differences in vulnerability or susceptibility to environmental and/or biological stress. The use of standardised behavioural, physical and pharmacological probes, using appropriate and ecologically valid stimuli, to assess individual differences in the responsibility of the maternal and/or fetal endocrine and immune systems at various time points over the course of gestation may prove useful in identifying individuals who may be particularly susceptible to the effects of stress and/or infection in pregnancy.

Thus, in conclusion, there is an urgent and compelling need to arrive at a better understanding of the determinants of social disparities as well as biological mechanisms involved in preterm birth. The study of stress and infection in pregnancy and the adoption of a dynamic, biobehavioural systems approach holds great challenge and promise in our efforts to address this important problem.

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References

16 Kaufman JS, Cooper RF, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology 1997; 8: 621–628.
41 Pritchard CW, Teo PY. Preterm birth, low birthweight and the stressfulness of the household role of pregnant women. Social Science and Medicine 1994; 38:89–96.
54 Andrews WW, Hauth JC, Goldenberg RL, Gomez R, Romero R, Cassell GH. Amniotic fluid interleukin-6: correlation with upper genital tract microbial colonization and gestational age in women delivered after spontaneous


86 Petraglia F, Sutton S, Vale W. Neuropeptides and peptides modulate the release of immunoreactive corticotropin-releasing factor from cultured human


103 Piccinini MP, Romagnani S. Regulation of fetal allograft survival by a hormone-controlled Th1 and Th2-type cytokines. *Immunologic Research* 1996; 15:141–150.


