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Psychosocial stress in pregnancy and preterm birth: associations and mechanisms

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Abstract

Aims—Psychosocial stress during pregnancy (PSP) is a risk factor of growing interest in the etiology of preterm birth (PTB). This literature review assesses the published evidence concerning the association between PSP and PTB, highlighting established and hypothesized physiological pathways mediating this association.

Method—The PubMed and Web of Science databases were searched using the keywords “psychosocial stress”, “pregnancy”, “pregnancy stress”, “preterm”, “preterm birth”, “gestational age”, “anxiety”, and “social support”. After applying the exclusion criteria, the search produced 107 articles.

Results—The association of PSP with PTB varied according to the dimensions and timing of PSP. Stronger associations were generally found in early pregnancy, and most studies demonstrating positive results found moderate effect sizes, with risk ratios between 1.2 and 2.1. Subjective perception of stress and pregnancy-related anxiety appeared to be the stress measures most closely associated with PTB. Potential physiological pathways identified included behavioral, infectious, neuroinflammatory, and neuroendocrine mechanisms.

Conclusions—Future research should examine the biological pathways of these different psychosocial stress dimensions and at multiple time points across pregnancy. Culture-independent

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characterization of the vaginal microbiome and noninvasive monitoring of cholinergic activity represent two exciting frontiers in this research.

Keywords

Corticotropin-releasing hormone; gestation; inflammation; pregnancy; preterm birth; psychosocial stress; vagus nerve

Introduction

Preterm birth (PTB) is a significant and growing public health problem leading to increased neonatal morbidity and mortality and entailing substantial social and economic costs [51]. PTB is the leading cause of infant mortality in industrialized countries, accounting for 60% of perinatal mortality and about half of long-term neurological morbidity [36]. There is also mounting evidence linking PTB to health outcomes in adulthood [19]. Despite the identification of numerous determinants of PTB, only about half of preterm deliveries are preceded by a known risk factor [68]. Thus, prediction of PTB remains poor. Identification of novel risk factors and elucidation of the pathways linking risk factors to PTB are therefore crucial research priorities.

PTB is defined as delivery before 37 completed weeks of gestation. In 2004, the rate of PTB was 12.5% of live births in the USA [6] and 8.2% in Canada [76]. Distur bingly, PTB rates are increasing in many industrialized countries [50] and exhibit significant disparities across racial groups and socioeconomic strata [6, 53]. Preterm labor accounts for about half of all PTBs, whereas preterm premature rupture of membranes and iatrogenic causes each account for roughly a quarter. Preterm infants are at increased risk of respiratory distress, jaundice, hypoglycemia, and neonatal death, as well as developmental delays and needs for special education [94]. Annual costs for preterm infants in the USA are estimated at more than $26 billion. PTB also exacts an emotional and financial burden on parents, increasing maternal distress and depressive symptoms [6].

PTB is currently understood to be a complex process stemming from multiple risk factors including genetics, health behaviors, reproductive history, mental health problems, and medical disorders [37, 68]. A growing literature supports the role of psychosocial stress during pregnancy (PSP) in the etiology of PTB [4, 39]. PSP and PTB are connected through neuroendocrine, inflammatory, and maternal lifestyle and behavioral pathways [16, 26, 92]. However, there is as yet no consensus concerning (a) which measures of PSP are most strongly associated with PTB, (b) whether there are critical time windows for the effects of PSP on PTB, (c) the cumulative effects of chronic stress, and (d) the roles played by different pathways in mediating associations between maternal stress and birth outcomes. This selective review of the literature will address these knowledge gaps by assessing the published evidence on the association between PSP and PTB and will highlight established and hypothesized physiological pathways mediating this relationship.

Method

We searched the PubMed and Web of Science databases using the keywords “psychosocial stress”, “pregnancy”, “pregnancy stress”, “preterm”, “preterm birth”, “gestational age”, “anxiety”, and “social support”. Our original search returned 352 articles. To be considered for inclusion, studies needed to be presented in English and to have PTB or gestational age as an outcome. At least one of the following exposures was also required: stressful life events, perceived stress, anxiety, and social support. We considered original research reports of observational studies as well as narrative and systematic reviews. Relevant studies were also located by reviewing the reference list of selected articles. This left 107 articles from which we constructed the core of our literature review. In light of space limitations and because our goal was to construct a selective review illustrating key current issues in this literature rather than a comprehensive systematic and quantitative review, we do not reference findings from all articles in our literature search. However, we do provide a complete list of core references in Appendix 1.

PSP and PTB

Several indicators of PSP including stressful life events, perceived stress, and pregnancy-related anxiety have been associated with PTB [16, 25, 42, 46]. There is some understanding of the biological pathways underlying these links and how they vary across pregnancy, but it remains incomplete. Although results vary by dimensions targeted and timing of exposure, most studies demonstrating positive results have found moderate effect sizes, with risk ratios between 1.2 and 2.1 for the highest stress scores compared with the lowest across a heterogeneous range of stress measurement scales. The following sections summarize existing knowledge on the measurement of PSP and on its association with PTB.

Measures of PSP

Stress constitutes a psychophysiological consequence of any event challenging an individual’s capacity to cope. Stressful life events are situations likely to require some degree of coping in ongoing life adjustment, whereas perceived stress is defined as the degree to which situations in one ‘s life are appraised as stressful. Anxiety is a related subjective concept measuring individual psychological and physical manifestation of exposure to perceived stress. Anxiety is traditionally separated into state anxiety (an emotional response to stimuli perceived as dangerous, threatening, or stressful, typically experienced as tension, worry, or nervousness – or how one feels at a given moment, for example, because of an upcoming interview or test) and trait anxiety (the predisposition to react to a wider range of stimuli by experiencing anxiety – or how one feels generally) [67]. In this review, we examine self-reported subclinical measures of anxiety during pregnancy. Clinical anxiety disorders such as generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder and their comorbidity with major depressive disorder are also likely to impact on obstetric and neonatal outcomes [63], and addressing links between clinical disorders and PTB can further be complicated by the effects of psychotropic medication [2] and other forms of self-medication such as substance use. Consequently, the

study of clinical anxiety in the prediction of PTB adds a level of complexity that falls outside the scope of this review.

Research on PSP has examined the roles of both objective stress constructs (i.e., exposures measured independently of the individual's perception of them such as a death in the family, becoming unemployed, natural disasters, or war-related violence) and subjective measures of stress levels. Not surprisingly, these two concepts are moderately correlated with each other [23]. Studies have also explored the role of "pregnancy-related stress", i.e., stress and anxiety stemming from the pregnancy. Measures of pregnancy-related anxiety capture this concept by asking about fears and concerns specifically related to the pregnancy [24]. Other examples of pregnancy-related stress-ors include physical changes naturally associated with pregnancy, concerns about the experience of childbirth and parenting, and relationship strains due to pregnancy [44]. Examining the role played by pregnancy-vs. non-pregnancy-related stressors is crucial in understanding how psychosocial stress differs in pregnant women compared with other populations and clarifying what kinds of stressors have the strongest impact on birth outcomes.

Stressful life events, their timing, and perceived impact

Stressful life events during pregnancy have been associated with PTB or shortened gestation in some [22, 23, 42, 47, 69, 97] but not all [1, 32, 58, 60] studies. The studies we reviewed that found effects of stressful life events during pregnancy on PTB were conducted in several different countries, had sample sizes ranging from fewer than 200 to more than 8000, and used both cohort and case-control designs. As the techniques used in measuring stressful life events have been refined, timing within the pregnancy and subjective perception of stress have usually been found to be stronger predictors of PTB than objective event counts across pregnancy [46, 57]. This finding was supported by our review; of the four studies we reviewed on stressful life events that did not find effects, two looked at life events globally across the entire pregnancy and only one measured the perceived impact of life events. In one of the earliest studies of stressful life events and PTB that did find effects, Hedegaard et al. [42] found one or more life events assessed as highly stressful at 30 weeks but not at 16 weeks was associated with a lower gestational age at delivery and increased risk of PTB. No association was found for life events evaluated independently of their subjectively perceived impact. This latter finding helped researchers shift attention from event counts to perception of stressful life events. However, the first finding led authors to propose that timing of delivery is likely to be determined toward the end of pregnancy, but subsequent biological evidence has not supported this hypothesis. Specifically, the maternal hypothalamic-pituitary-adrenal (HPA) axis has been shown to be progressively downregulated over the course of pregnancy [84], suggesting that biological and emotional stress responses may be attenuated toward the end of pregnancy. In light of this evidence, it is not surprising that life events experienced at the beginning of pregnancy were perceived as more stressful than similar events occurring in the third trimester [34]. A later prospective cohort study supported this view and found that after adjustment for confounders, life events perceived as severely stressful were only associated with PTB when experienced during the first and second trimesters of pregnancy but not the third [97]. Thus, this epidemiological study failed to replicate the finding of Hedegaard et al. regarding exposure to stressful life events later in

pregnancy and found instead that earlier exposure was more likely to be associated with PTB.

Studies of pregnant women exposed to traumatic acute events also support this view. In a retrospective cohort study of women who were pregnant during or after a 1998 ice storm in Quebec, Canada, Dancause et al. [18] found a trend toward shorter gestational age at delivery among women in the first or second trimester of pregnancy at the time of the ice storm compared with those who were in the third trimester or became pregnant within 3 months following the storm (when stress hormone levels could still be elevated). In a similar study examining timing in relation to pregnancy of a 1994 California earthquake and length of gestation, earlier exposure was significantly associated with shorter gestation [35]. Other studies assessing the effects of acute exposure to natural disasters, war, and terrorism during pregnancy have also found these stressors to present highest risk early in pregnancy. In sum, observational research supports a stronger role for subjectively perceived stress in the prediction of PTB compared with objectively defined stressful events as well as a stronger role for stressors experienced early compared with later in the pregnancy [46, 57].

General perceived stress and maternal anxiety

An important limitation of the “ life event “ approach to stress in PTB research is that it often fails to capture relevant chronic stressors such as racism, domestic violence, and less severe “daily hassles”. In contrast, the assessment of perceived stress is not necessarily tied to specific events and is thus likely to capture individuals’ actual stress levels more precisely than objective scales of stressful life events [46]. Measures of anxiety also share this advantage in that they are not bound to specific events experienced by an individual.

Both anxiety and general perceptions of stress (independent of its source) have been associated with shortened gestation in many [22, 32, 58, 66, 71, 78, 79, 81, 87] but not all [1, 49] studies. Our review revealed that studies with null findings tended to be characterized by study populations of higher socioeconomic status and exposure measurement scales not specific to pregnancy. Trait anxiety measures have generally not shown strong direct relationships with birth outcomes, which is likely because they are not sensitive to the presence of stressful stimuli that may trigger state anxiety [59]. Some studies have in fact found protective effects for trait anxiety [7, 77], which may be attributable to a cautious attitude regarding problems or complications arising during the pregnancy. Trait anxiety has, however, shown positive correlations with shortened gestation when combined with more severe risk factors. For example, an inverse correlation between trait anxiety and gestational duration was observed in a study of Swedish women who were in the first trimester of pregnancy at the time of exposure to a clear acute stressor, the Chernobyl nuclear disaster [55].

In contrast to trait anxiety, several studies have found positive associations between pregnancy-related anxiety and PTB or shortened gestation [22, 71, 77, 93]. One prospective cohort study found pregnancy-related anxiety to be associated in a dose-response fashion with increasing adjusted odds of spontaneous PTB [71], whereas another prospective study found an increased risk of PTB among women with high levels of pregnancy-related anxiety and among those who experienced life events with perceived negative impact [22]. In an

attempt to examine both trait anxiety and pregnancy-related anxiety independently, one study found pregnancy-related anxiety was associated with an increased risk of PTB, whereas a protective effect was observed for trait anxiety [77]. Overall, when it comes to risk for PTB, our review suggests that pregnancy-related anxiety may in fact contribute more powerfully to adverse birth outcomes than non-pregnancy-related stressors and that it is a more consistent predictor of PTB than other prenatal stress measures.

Effects of social support

One promising avenue of inquiry in pregnancy research is the possibility that social support may buffer the impact of PSP. Social support is defined by the exchange of social resources between individuals. Although research on the relationship between social support and physical and mental health has been complicated by great heterogeneity of measurement, there is broad consensus on the conceptual division of social support into emotional, informational, and instrumental support [17, 72]. Social support has been hypothesized to affect health through pathways that are relevant to PTB including changes in health behaviors and increased resistance to infection [72].

Social support is conceptually understood to affect health both through direct mechanisms and by buffering the association between stressors and health [71]. Social support has been found to influence perceived stress in pregnant women [86], and it has been hypothesized that social support could mitigate the impact of PSP on PTB. Epidemiological studies have shown inverse correlations between social support and stress biomarkers (e.g., adrenocorticotropin hormone, β-endorphin, cortisol) in pregnant women [91], suggesting that the effects of stress during pregnancy on birth outcomes may be amenable to intervention. However, research examining the relationship between social support during pregnancy and birth outcomes has yielded disappointing results, with numerous null findings in both observational studies and clinical trials looking at PTB [10, 66, 72, 90]. Positive results have been observed in a small number of studies. One case-control study examining paternal support found a trend toward reduced PTB and buffering of the effect of chronic stress among women with higher levels of partner support [32]. A randomized trial of nurse home visitation found a reduced rate of PTB in two high-risk subgroups of the intervention arm, smokers and young adolescents [70]. Another positive subgroup finding was observed in an intervention trial of paraprofessional home visit support to pregnant teenage women. This study found a reduction in PTB among unmarried mothers in the intervention group [80]. Importantly, mothers in the intervention group were more likely to receive adequate prenatal care than those in the control group, yet the effect of the intervention on PTB persisted after adjustment for adequacy of prenatal care. This suggests that in certain high-risk populations, effective social support interventions can improve birth outcomes both through health care services (likely in response to informational support) and *via* more direct pathways that may stem from emotional or instrumental support. Overall, in light of the scattered positive findings in this area, further research is needed to clarify the effects of women's existing social support on PTB. That research could address what components would make up the most promising social support interventions and which populations should be targeted.

Combined exposure measures

Different dimensions of PSP are correlated with each other [45, 57, 78, 79], suggesting that the various measures capture overlapping domains. To account for this intersection, some investigators have combined multiple exposure concepts into latent variable constructs. One such study used structural equation modeling techniques to combine state anxiety, perceived general stress, life events, and pregnancy-related stress into a single latent variable. The latent stress factor significantly predicted gestational age at delivery, although pregnancy-related stress was a better predictor than the latent factor [58]. In an earlier cohort study [59], prenatal stress was operationalized using a combination of perceived stress, state anxiety, and life events. This latent variable significantly predicted timing of delivery. In one prospective study examining several measures of anxiety and personal resources [78], state anxiety and pregnancy-related anxiety were loaded on a single factor labeled “stress “ that was found to be significantly correlated with length of gestation and was predictive of PTB. Finally, a study combined perceived stress, state anxiety, and pregnancy-related anxiety, each measured at three time points across pregnancy, using a longitudinal latent trait-state model [79]. In this study, only pregnancy-related anxiety experienced throughout the course of pregnancy was associated with shorter gestation after controlling for known risk factors.

Mechanisms linking PSP with PTB

Biological mediators of the relationship between PSP and PTB include neuroinflammatory, immune, and neuroendocrine pathways [26, 44, 46]. In addition, stress-related behaviors including smoking, substance abuse, and poor nutritional intake have been implicated in the etiology of PTB [26]. Finally, pregnancy-related anxiety may sometimes stem from medical risk that itself leads to PTB. Figure 1 provides a partial schematic of the key variables connecting PSP to PTB through the pathways discussed below.

Research directly exploring biological and behavioral mechanisms mediating the relationship between PSP and PTB is scarce. Rather, these mechanisms must at present be triangulated from epidemiological studies and research conducted using animal models. The few studies that have attempted to describe connections between psychological stress, biological stress markers, and PTB have generally examined PTB prediction models using both types of stress measures concurrently [74, 82] or have reported inconclusive results when connecting both types of stress measures with birth outcomes [41, 43, 83].

Hormonal and neurological correlates of psychosocial stress

The biological manifestations of stress have been assessed from hormone levels in tissue samples as well as through measurement of dopaminergic activity and prefrontal functional connectivity using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scans [54, 56]. For example, experimentally induced mild psychosocial stress has increased dopamine release and dopaminergic activity in the prefrontal cortex (PFC) [54]. Importantly, stress was associated with reduced attention control and functional connectivity in the PFC in a manner persisting beyond the experience of acute stress but that was reversible in response to reduced chronic stress [56].

Psychosocial stress is generally understood to positively correlate with salivary cortisol. Stress is also often directly correlated with corticotropin-releasing hormone (CRH), although negative results have been observed in late pregnancy and inverse correlations were found with chronic stress. Experimental introduction of chronic psychosocial conflict has also been shown to reduce CRH binding sites in the brain of adult tree shrews [29].

Effects of chronic stress

Results from both animal and human studies show associations between psychosocial stressors and alterations in the amygdalic and hippocampal reaction to novel stressors as well as with elevated serum CRH levels and CRH gene expression in the amygdala. This suggests the hypothesis that chronic stress may prime an individual to an adaptive state of hypervigilance and by a process of sensitization increase the physiological responses to future acute stressors [61]. Conversely, chronic stress is also hypothesized to blunt HPA function and has been shown to desensitize the stress response in the entorhinal cortex and striatum of adult rats exposed to chronic prenatal stress [30]. Finally, chronic stress increases susceptibility to infection and is associated with maternal infection during pregnancy. In sum, the relative contribution of chronic vs. acute stress to PTB requires further research.

Neuroinflammatory pathways

Inflammation is the basic process by which tissues of the body respond to injury through the effects of cytokines and other inflammatory mediators. Cytokines are small soluble peptides or glycoproteins including interleukins (ILs), chemokines, and tumor necrosis factor (TNF), among others. Cytokines' primary function is intercellular communication, and their role in the inflammatory response functions largely through regulation of the immune response [38]. PSP is hypothesized to bring about parturition in part through proinflammatory mechanisms [37], specifically proinflammatory cytokines [15]. As alluded to above, conclusive links connecting psychosocial stress, inflammation, and PTB have not been demonstrated.

However, a considerable body of evidence supports this mediation hypothesis. For example, psychosocial stress leads to increased production of proinflammatory cytokines in the general population [16], and altered levels of inflammatory cytokines have been observed in pregnant women with increased psychosocial stress [16, 92]. Although the precise effects of PSP on the inflammatory response during pregnancy and subsequent birth outcomes have not been precisely described [16], it has been shown that an inflammatory response in the form of overexpression of toll-like receptors in the chorioamniotic membranes is part of normal term labor [8]. Further supporting the role inflammation in parturition, inflammatory cytokines increase the production of prostaglandins, which are implicated in term and preterm labor [12]. Through induction of matrix metalloproteinases, inflammatory cytokines can also weaken fetal membranes and ripen the cervix [85]. A recent meta-analysis found that the inflammatory cytokine IL-6 and C-reactive protein were strongly associated with spontaneous PTB [95], and biological evidence also supports the role of TNF-α in preterm parturition [38]. In addition to the role of the inflammatory response in spontaneous PTB, inflammation has also been causally linked with indications for induced preterm delivery (hypertensive disorders of pregnancy). Specifically, features of preeclampsia such as

adipocycte lipolysis, *de novo* hepatic fatty acid oxidation, and impaired prostacyclin and nitric oxide production can be induced by inflammatory cytokines, and the clinical severity of preeclampsia has been associated in a dose-response fashion with cytokine function [16, 73].

Recent work has begun to describe a cholinergic anti-inflammatory pathway (CAP) in which the release of inflammatory cytokines is controlled through the vagus nerve. Specifically, action potentials transmitted through the vagus nerve result in the release of acetylcholine, which inhibits cytokine production by innate immune cells in tissues innervated by the vagus nerve. Evidence in support of this pathway comes from suppression of inflammation (decreased production of proinflammatory cytokines with no change in production of anti-inflammatory cytokines) in response to stimulation of the vagus nerve in adult animal models [88]. Specifically, vagus nerve stimulation inhibits inflammatory cytokine production in an adult rat model of sepsis [9], in a mouse model of pancreatitis [89], and in postoperative ileus [20]. In addition, clinical-pathological studies in adult human subjects with chronic inflammatory conditions show that increased spontaneous CAP activity is correlated to decreased levels of proinflammatory cytokines such as IL-1β.

The relevance of this line of research to the link between PSP and PTB is suggested by results showing a dampening of the connection between inflammation in response to decreased vagal nerve activity and depression (i.e., mouse model studied through monoamine depletion and maternal separation) [31]. This line of work is beginning to map out connections between the brain and inflammatory response that could provide a crucial link connecting neural responses to stress during pregnancy with inflammation-mediated adverse birth outcomes. Of note, CAP activity can be monitored non-invasively *via* heart rate variability (HRV) derived from maternal or fetal ECG. This opens a new, very cost-effective venue for exploring the relationships among PSP, maternal and fetal CAP, inflammation, and PTB in prospective clinical studies.

Infectious pathways and maternal microbiome

Infection is a well-documented risk factor for PTB and is likely to partially mediate the relationship between PSP and PTB. Bacterial vaginosis, the most common lower genital tract infection in women of reproductive age, is associated with stress in pregnant women and with a 1.5- to 3-fold increase in risk for preterm labor. However, the current characterization of intrauterine infection is imprecise. Numerous different bacteria are known to comprise the vaginal flora, yet clinical tests for infection rely on measures that are relatively crude and sometimes inconsistent, and intrauterine infections during pregnancy are frequently subclinical and escape diagnosis. Furthermore, many intrauterine infections are caused by bacteria that resist cultivation, thus limiting the utility of culture-based detection.

Culture-independent detection methods are becoming more common and are enabling a more advanced understanding of the genetic content of the vaginal microbial community, known as the vaginal microbiome. Through the NIH's Human Microbiome Project, research is showing the vaginal microbiome to be more diverse and complex than previously suspected [21, 96]. Improvements in DNA sequencing will enable detailed characterization of these infectious bacteria. However, current knowledge of the vaginal microbiome in

pregnant women is limited, and research connecting the maternal microbiome with prenatal stress and birth outcomes is in its infancy. However, there have been substantial advances attained in the characterization of the intestinal microbiome and elucidation of its relationship with the central nervous system. This progress is promising. For example, psychosocial stress has been shown to alter the composition of the intestinal microbiome. Specifically, prenatal stress in rhesus monkeys has resulted in reduced gut concentrations of lactobacilli (the most prevalent of the lactic acid-producing bacteria that dominate the vaginal flora of healthy women) in their newborn offspring [5]. Should this pattern translate to the maternal vaginal microbiome as well, it would provide important insights into the biological pathways mediating infectious causes of PTB and their relationships with the maternal nervous system's response to psychosocial stress.

In pregnant women, psychosocial stress is thought to modulate the immune response. Inflammatory and infectious pathways to PTB are linked together, as the immune and inflammatory responses influence each other reciprocally. In cases of infection, the inflammatory response serves to initiate an immune response to control the infection.

Neuroendocrine pathways

The maternal HPA axis constitutes the principal neuroendocrine mechanism mediating the link between PSP and PTB [26]. In pregnancy, maternal cortisol stimulates placental gene expression that increases placental CRH production. Although cortisol inhibits maternal hypothalamic CRH production, placental CRH production increases maternal CRH and also stimulates maternal adrenal cortisol secretion, creating a feedback loop. Ultimately, maternal CRH concentrations increase 20-fold across the course of pregnancy [46, 91], peaking at labor and delivery.

Epidemiological evidence strongly suggests that maternal cortisol is correlated with PTB [33]. Cortisol contributes to increased prostaglandin production and downregulation of prostaglandin-metabolizing enzymes, which accelerate paracrine and autocrine aspects of parturition [13, 14]. It is likely that CRH also plays a role in the association between PSP and PTB. Although it has been hypothesized that CRH is a noncausal marker for PTB [52], several plausible hypotheses suggest CRH to play a causal role in the initiation of parturition. CRH promotes fetal prostaglandin production, leading to premature myometrial contractility. In addition, CRH stimulates fetal and steroid hormone output, leading to placental estrogen biosynthesis and subsequent myometrial activation [11]. CRH is also linked with activation of the fetal HPA [8], leading to uterine activation [14]. Of note, CRH measurements have been able to distinguish patients presenting in preterm labor who deliver preterm from those who go on to deliver at term [11, 48], suggesting that term and PTB have differing neuroendocrine underpinnings.

PSP, CRH, and PTB

CRH is one mechanism hypothesized to function as a "placental clock" controlling parturition, and CRH trajectories across pregnancy have predicted timing of delivery [65]. There is some evidence linking PSP with maternal CRH. Although the precise links among maternal stress, CRH, and parturition remain unclear, an emerging body of research has

begun to explore these relationships and to advance and test hypotheses regarding neuroendocrine mechanisms connecting PSP and PTB.

In one study, at 28–30 weeks' gestation, the effect of pregnancy-related anxiety on gestational age became nonsignificant after controlling for CRH level, that is, CRH appeared to mediate the relationship between anxiety and gestational age at delivery [62]. However, other studies have failed to find associations between stress or anxiety and maternal CRH. One study of women in midpregnancy found job stress and stressful life events were unrelated to serum CRH at 28 weeks' gestation [75]. An additional study found an association between perceived stress and PTB; however, perceived stress was unrelated to maternal CRH as measured at the second trimester [43].

In contrast to these negative findings, moderating effects have been observed between stress and CRH on PTB in two studies. In one study, Guendelman et al. [40] found that the effect of CRH on preterm delivery was stronger in women exposed to chronic stressors during pregnancy compared with unexposed women. In a second study, Hobel et al. [45] compared women delivering preterm with matched term deliveries, finding a positive association between perceived stress and maternal plasma CRH for the PTB cases but a negative association for controls. Interestingly, stress was also inversely associated with CRH in the study by Guendelman et al. [40], who hypothesized that reduced CRH may be a protective response on the part of the placenta to prolong gestation in cases of stress.

Taken together, these results suggest that CRH does not consistently mediate or modify the association between PSP and PTB. However, as both psychosocial stress and elevated CRH levels and rates of increase across pregnancy have been frequently associated with PTB, it is likely that psychosocial stress interacts with maternal CRH to shorten gestation in some cases. The studies by Guendelman et al. [40] and Hobel et al. [45] provide preliminary support for this hypothesis.

Limitations

Several relevant exposures fall outside the scope of this review. As discussed above, we did not include clinical anxiety disorders in our discussions of maternal anxiety. We also did not delve into research examining the role played by maternal age in PTB, and we did not examine several other diverse types of stressors such occupational stress and oxidative stress. Studying the links between these forms of stress and PTB requires substantially different tools and study designs from the research targeted by our review. Finally, we did not examine the impact of depressive symptoms or clinical depression. Although anxiety and depression bear some overlapping features, they are separate conditions, both at clinical and subclinical levels. As several studies have found anxiety and depression are most likely to impact on pregnancy outcomes when comorbid [27, 28], future research on clinical and subclinical levels of these conditions during pregnancy should clarify their independent and synergistic effects.

Summary and future directions

PTB is a significant and growing public health problem entailing substantial medical, social, and economic costs. Despite steady scientific progress leading to improved understanding of its risk factors and underlying physiology, PTB rates have not declined and are in fact increasing globally. A robust and growing body of research supports the role of psychosocial stress as an etiological risk factor for PTB. Set against a context of poor prediction coupled with increasing incidence of PTB, the importance of psychosocial stress is further highlighted by its potential amenability to intervention. Psychometric research has made significant advances in identifying the most sensitive tools to measure PSP, while clinical research has begun elucidating the interlocking biological pathways connecting PSP with PTB. In reviewing the current knowledge base on PSP and PTB and the role played by neuroinflammatory, infectious, and neuroendocrine pathways in this relationship, several major findings and promising future research directions emerge.

Research to date on PSP has used many related and overlapping stress and anxiety measures. Although trait anxiety could have protective effects against PTB, perceived stress and pregnancy-related anxiety appear to be the stress measures most consistently associated with risk for PTB. These findings support the study of prevention strategies aimed specifically at pregnancy-related anxiety and perceived stress in randomized clinical trials of pre-natal intervention programs. To continue informing such efforts, future research must study these exposures and their reduction at multiple time points across pregnancy.

Further work is also needed to clarify the role played by maternal age-related stressors. Associations have been observed between PTB and both extremely low and high maternal age [3, 64], and research on stress and birth outcomes tends to treat maternal age as a potential confounding variable. It is readily plausible that maternal age could be associated with some forms of psychosocial stress and that stress may therefore be a mediating pathway that accounts for some of the link between maternal age and PTB. However, research to date has not distinguished the roles played by biological age, previous pregnancies and family stresses. Future work exploring age-related stressors in pregnancy will need to use study designs that take into account these factors.

Neuroendocrine biomarkers including cortisol and CRH provide important insights into the role of the neuroendocrine system in the initiation of parturition and the relationship between PSP and PTB. Inflammation and infection are other key mediating factors in this relationship. Although these physiological pathways have not conclusively explained the connection of psychosocial exposures to PTB, several novel advances show considerable promise in this area. For example, the ability to monitor CAP activity *via* HRV presents an exciting possibility for the safe and inexpensive exploration of the link between stress and inflammation and the role of inflammation in term and preterm parturition. Characterization of the structure and function of the maternal microbiome will enable a clearer and richer understanding of the role played by infection in the relationship between stress and length of gestation. Research joining the fields of psychometrics, epidemiology, and clinical obstetrics points toward promising possibilities for future interventions to prolong gestation where appropriate and reduce the rate of PTB.

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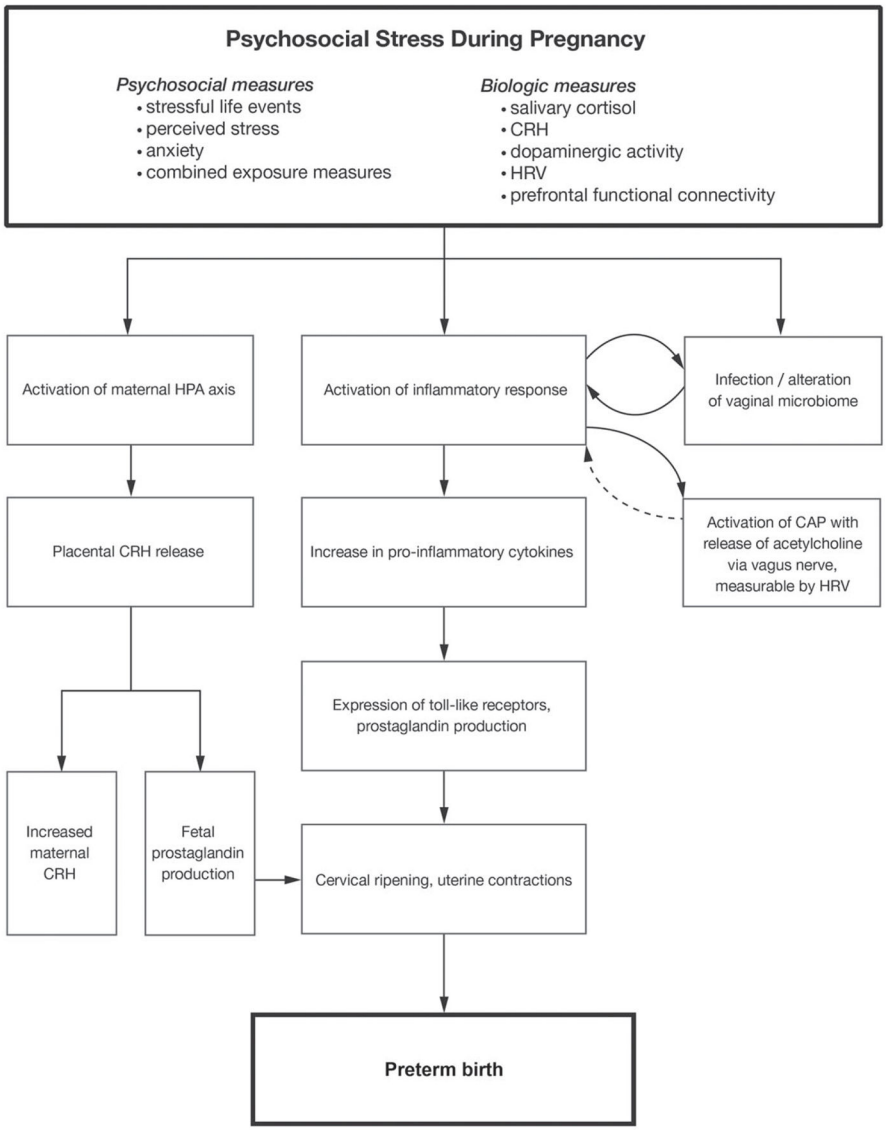

Figure 1.

Key physiological pathways connecting PSP to PTB.

Solid arrows=known or hypothesized causal relations; solid curved arrows=positive feedback loops; dashed arrows=negative feedback loops.