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1. Introduction

Stress is defined as a physiologic response to psychological and physical demands and threats [1]. That is - when “environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease” [2]. Despite the challenges of measuring, defining, and studying stress, a large body of literature documents the contributions of stressors and affective state during pregnancy on birth outcomes [3]. In the last two decades, psychosocial stress has evolved to encompass mental health states and stressors such as anxiety, depression, racism, lack of social support, coping mechanisms, job strain, acculturation stress, and domestic violence [4].

In general stress is divided into acute and chronic stress. While stress may have some benefits in responding to stressors, chronic stress has been shown to be associated with chronic diseases including preterm birth. Acute stress is short-lived, an effective resolution to heightened threats or demands [1]. Examples of acute stresses can be impending final exams for college students, brief relationship arguments, and minor upsets in finances. Chronic stress persists for longer period of time without resolution to threats or demands. Stressors that accompany social racism, prolonged homelessness, living in sub-standard conditions, living in high crime rate neighborhoods, and being a single parent are long-standing and chronic.

Mounting evidence has linked stress to multiple chronic diseases over the years. This is particularly true in studies investigating preterm births. Preterm birth is one of the leading causes of infant mortality and childhood morbidities and it is mainly caused by premature rupture of membrane. Although some of the factors leading to premature births are known, the cause for early labor is not fully understood. In the past decade, the influence of stress on premature birth has received special attention. This chapter discusses the role of stress as it relates to preterm birth. Additionally, the patho-physiologic mechanisms, risk factors, and psychometric measures and biomarkers used to assess stress are examined.
2. Poor birth outcomes and stress

Preterm and low birth weight, and intrauterine growth restriction are the leading causes of neonatal and infant morbidity, mortality, and neurodevelopmental impairments worldwide [5,6]. A preterm birth is the birth of an infant less than 37 weeks of gestation. Preterm birth contributes to other adverse birth outcomes such as low birth weight (defined as 2,500 grams or less), developmental delays, infections and cognitive impairment [7]. An extensive body of research provides evidence for the relationship between stress and poor birth outcomes such as prematurity and low birth weight. Other adverse health sequelae such as birth defects, miscarriages, stillbirth, and maternal complications (i.e. preeclampsia, gestational diabetes, and prenatal hemorrhaging) are also associated with maternal stress [8-11]. Occurring in 8 to 12 percent of all pregnancies worldwide, rates of preterm birth and low birth weight are higher in the United States compared to other industrialized nations [12]. Despite efforts to improve birth outcomes, preterm birth and low birth weight remain a major issue due to increasing disparities in rates [13]. Moreover, certain subgroups are disproportionately affected by the problem. For instance, in the U.S., African-Americans have almost twice the rate of low birth weight and preterm delivery, and three times the rate of very low birth weight (<1,500 grams) and very preterm delivery (<32 weeks) compared to Caucasian Americans [14]. High rates of prematurity and low birth weight are of public health concern because they are the leading causes of infant and neonatal morbidity and mortality [15]. Preterm infants are at higher risk for serious complications such as respiratory, gastrointestinal, nervous system, and immune-related problems [7].

2.1. Preterm birth

The first study to explore the relationship between stress during pregnancy and development biology took place in the 1940’s with the advent of Sontag’s pioneering work [16]. Sontag observed a relationship between emotional disturbance in pregnant mothers and hyperactive fetuses and early feeding difficulties in their offspring. More than two decades later, Gunter published a report on stressful environmental and psychological factors before and during pregnancy and preterm birth among Afro-American women [17]. Twenty cases of women who experienced preterm birth were matched with 20 women with normal deliveries. Gunter conducted a thorough evaluation using a battery of assessments that included measures of self-concept, psychosomatic and neuropsychiatric symptoms, and life events related to death in the family, desertion, economic need, and physical disabilities. Results implied a relationship between psychosomatic conditions and life or social situation of the mother were related to the outcome of pregnancy. Until the 1990’s, many investigations on stress and preterm birth were largely retrospective, riddled with weak conceptualizations and methodological problems that limited conclusions [18]. Since then, the body of research on psychosocial stress and preterm has grown substantially, and though there are conflicting reports, studies have shown that women experiencing high stress are 1.5 to 3 times more likely to experience preterm delivery than less distressed women [7,19,20].
Dole and colleagues conducted a study to examine a comprehensive panel of psychosocial factors among which included negative life events, pregnancy-related anxiety, and other stressors in relation to preterm birth in a prospective cohort study of nearly 2,000 pregnant women in North Carolina [21]. They found that women in the highest negative life events impact quartile had the highest risk of preterm birth (adjusted RR = 1.8, 95% CI = 1.2 to 2.7). Further, pregnancy-related anxiety in mid-pregnancy predicted spontaneous preterm birth even after controlling for a wide range of confounding variables (RR = 2.0, 95% CI = 1.6 to 3.9). There is converging evidence across studies of diverse populations regarding the adverse effects of pregnancy anxiety on preterm birth [3]. Pregnancy anxiety, defined as fears and anxiety related to the health and well-being of the baby, childbirth, and postpartum parenting, predicts the risk of spontaneous preterm birth with consistent results for various racial and ethnic groups [3,22].

Dunkel Schetter and Glynn conducted a systematic review for the relationship between various types of stress and preterm birth [23]. This comprehensive study included more than 80 studies of which most had prospective designs with robust sample size and validated measures. Authors reported that stressful life events, major community-wide disasters, chronic stressors, and pregnancy anxiety increased the risk for preterm birth. Of the studies assessing major life events during pregnancy, more than half reported significant effects on gestational age or preterm birth. Women who experienced stressful life events such as the death of a family member were 1.4 to 1.8 times as likely to have a preterm birth. Similar to other studies, the estimate of effect was stronger when stressful life events took place earlier in the pregnancy. Other types of stress brought on by natural disasters or terrorist attacks, chronic strain (i.e. general, household, homelessness), and neighborhood stressors (such as poverty and crime) also contributed independently to the risk of preterm birth or gestational age. Although studies that used standard scales to measure daily hassles showed no significant effect on birth outcomes, using combinations of perceived stress measures predicted preterm birth in some studies [15,24,25].

Two main factors have emerged as central in better understanding the impact of life event stressors on preterm birth: timing of stressor and self-perceived stress [26]. Several studies have shown a decline in psychological and physiological stress response in pregnant women as pregnancy progresses [27-30]. A paper published in 2001 by Glynn and colleagues reported that women who lived through the Northridge earthquake in California showed a differential response to the psychological effect of the earthquake depending on their gestational age at the time of the event [28]. There was a significant association between women who experienced the stress early in the pregnancy and shorter gestational age at delivery. Participants in the first trimester also evaluated the earthquake as more upsetting and aversive than women in the second or third trimester scoring higher on a life events inventory. Similar results were observed among women who lived through the aftermaths of the terrorist attacks at the World Trade Center on September 11, 2001 [31]. Women who were in their first trimester at the time of the stressful incident showed shorter gestational times than controls; however no difference was observed among women in the second trimester. Considering the time frame of maternal...
exposure to stress and self-perceived severity of stress may be important in understanding how women’s response to stress has an impact on fetal development.

### 2.2. Low birth weight

Chronic stressors are robust predictors of low birth weight, infant weighing less than 2,500 grams at birth [32]. Although a significant proportion of low birth weight infants are preterm births, several studies have reported the impact of stress on low birth weight. A recent population-based cohort study conducted by Brown et al. sought to examine the social determinants of low birth weight in Australia [20]. One in six women reported three or more stressful life events or social health issues in the 12 months preceding the last birth. Women coping with multiple life events remained significantly more likely to have a low birth weight infant after adjusting for smoking, number of prenatal visits, and other known covariates. Specifically, women reporting three or more stressful events or social health issues had a twofold increase in odds of having a low birth weight infant compared to women reporting no issues. In a U.S. study, maternal stress was associated with 2 to 3.8 times the risk of low birth weight among a sample of nearly 1,400 pregnant low-income women [33]. In fact, there is a 55-gram reduction in infant birth weight or low birth weight for every unit increase of stressful life event [34]. Similar results have been observed elsewhere in European countries [35-37].

In Amsterdam, Paarlberg et al. recruited almost 400 women from several obstetric outpatient clinics to conduct a prospective study on stressors and low birth weight [36]. Questionnaires on daily stressors, psychological and mental well-being, and social support were completed by women throughout their pregnancy. Having experienced daily stressors in the first trimester was associated with an increased risk of low birth weight. Indeed the relationship was strongest when multiple exposures interacted to contribute to a compromised fetal growth. In Scotland expectant mothers perceiving high levels of household stress at 20 weeks gestation had increased odds of low birth weight (OR = 4.7, 95% CI = 1.5 to 13.4) [35]. Results from the Scotland study suggests that the relationship between psychosocial stress and low birth weight may be attributable to variation in energetic intake and expenditure. For example, pregnant women who carry the burden of running a household without the support of a husband or partner may suffer inadequate nutritional provisioning and greater workload, reducing maternal and fetal weight gain.

Overall, preterm birth and low birth weight are commonly studied together as tandem outcomes because infants born preterm are often of low birth weight. It has been estimated that two-thirds of low birth weight infants are born preterm [3]. Prior work in the field had the tendency to combine various psychological processes into one psychosocial category that typically consisted of stress, emotions, coping, social support, and more. However, a growing body of research supports differences in the psychological processes involved in the etiology of both birth outcomes [23,25]. While pregnancy anxiety appears to be a strong predictor of preterm birth, depression and chronic strain appear to be stronger predictors of low birth weight [23]. Epidemiologic and social behavioral studies on the psychological pathways contributing to these two birth outcomes deserve individual attention. Disentangling the
components of psychological processes may lead to improved intervention models for at risk populations and better inform health policies that seek to reduce preterm and low birth weight. Defined as “cognitive and behavioral efforts to manage stressful demands” coping may directly affect birth outcomes, minimize perceived stress, or modify the effects of stress on birth outcomes [23]. However, very little studies exist on the relationship between birth outcomes and coping during pregnancy. A direction for future research may be to consider various coping processes in pregnancy and strategies to effectively reduce anxiety and understand resilience in the face of adversity.

3. Mental health and stress

Stress plays an important role in the development and worsening of mental illness such as depression or anxiety disorders [38-41]. Depression and anxiety are approximately twice as prevalent globally in women as in men [42]. Approximately one in five women will experience depression during her lifetime with the typical age of onset during the reproductive years [43,44]. Estimates on the prevalence of antenatal depression, or depression during pregnancy, can vary depending on the criteria used but can be as high as 16 percent with increasing proportions in the year following delivery [42,45]. The contribution to the Global Burden of Disease (GBD) of only three mental disorders (i.e. mood disorders, schizophrenia and specific anxiety disorders) among women aged 15 to 44 years is seven percent of the total GBD for women of all ages [46]. In fact, depression is fourth among all causes of GBD for women and is expected to rank second by the year 2020.

There has been a growing interest in the potential etiologic association of psychosocial factors, including maternal depression with birth outcomes given a number of studies that support the relationship between stress and maternal depression [47,48]. For example some studies have highlighted the key role of maternal depressive symptoms and general distress during pregnancy on reduced fetal growth, low birth weight and preterm birth [48,49]. The impact of maternal mental disorder on infants goes beyond just delayed psycho-social development but has severe health consequences that are of considerable concern in developing countries. Postpartum non-psychotic depression is the most common complication of childbearing affecting about 10 to 15 percent of all women [50]. The perinatal period is a time of increased physical and emotional demands on expectant or newly mothers and the disability associated with depression can interfere with many essential functions related to both the mothers and infant. Maternal mental health has been associated with reduced breast-feeding, severe malnutrition, stunted growth, increased episodes of diarrhea and lower compliance with immunization schedules [46].

Psychiatric research on pregnancy has largely focused on diagnosable mental disorders such as anxiety and depressive disorders and posttraumatic stress disorder following negative life events or experiences [51]. However, scientific research outside psychiatry has also provided useful information on clinical symptoms during pregnancy using tools such as the Edinburgh Postpartum Depression Scale (EPDS), Beck Depression Inventory, or the Center for Epide-
miological Studies Depression Scale [51]. Scores are commonly kept continuous to evaluate symptom severity or often dichotomized to create groups of depressed and non-depressed women as proxy for diagnosed cases. Current understanding of negative affective states during pregnancy and its impact on birth outcomes is mostly based on studies of symptomatology rather than on confirmed diagnoses.

In a recent review, anxiety during pregnancy was identified as a significant predictor of gestational age and preterm birth in seven of 11 studies [23]. Results were more consistent for pregnancy anxiety or pregnancy-specific anxiety which, unlike general state anxiety, is a distinct syndrome reflecting fears about the health and well-being of one’s baby, pregnancy, childbirth, and postpartum parenting. One large prospective study of 4,885 births found that women with high pregnancy anxiety had 1.5 times greater risk of a preterm birth after controlling for confounders [22]. Furthermore, pregnancy anxiety predicts risk of spontaneous preterm birth with effect sizes comparable to the effects of known risk factors such as smoking and medical risks [51].

Prior findings on the relationship between antenatal depression and gestational age or preterm birth have been relatively inconsistent and inconclusive [52]. Dunkel Schetter and Glynn reported that 11 out of 14 reviewed studies showed no effect on gestational age due to depressed mood or symptoms of trauma. Furthermore, the three studies that reported association had some methodological limitations [23]. One study from the U.S. had a small sample size of 120 rural women between 16 to 28 weeks gestation and depression symptoms was determined by two screening items [53]. Another study took place in France where 634 pregnant women were assessed using self-administered questionnaires to determine anxiety and depression. Depression was positively associated with spontaneous preterm labor but with large confidence intervals and only among women with a pre-pregnancy body mass index of less than 19 (adjusted OR = 6.9, 95% CI = 1.8 to 26.2) [54]. In a large study, Orr et al. found that women with an elevated depressive symptom score had 1.96 times the odds of experiencing spontaneous preterm birth compared to women with a lower score (95% CI = 1.04 to 3.72) [55]. This U.S. study had a large sample size of 1,399 but only African-American women were included in the study [55].

Due to the conflicting results and limitations related to methodological designs, sample size, biases, and populations studied, Grote et al. conducted a thorough meta-analysis of antenatal depression and the risk of preterm birth, low birth weight, and intrauterine growth restriction [56]. Prospective observational studies in English and non-English languages from 1980 to 2009 were compiled for consideration. A total of 29 articles were included in the analysis. Twenty studies evaluated the association between antenatal depression and preterm birth with relative risk estimates ranging from 1.01 to 4.90. Eleven of the studies showed no significant association but using a random-effects model, depression during pregnancy was significantly associated with preterm birth (RR = 1.13, 96% CI = 1.06-1.21). Furthermore, there was a slightly increased risk for low birth weight (RR=1.18, 95% CI = 1.07-1.30). Thus, antenatal depression, regardless of the type of depression measurement (categorical or continuous) was associated with modest but significant risks of preterm birth and low birth weight. Further, based on categorical measures of antenatal depression, having major depression or clinically significant depressive...
symptoms increased the risk of preterm birth by 39%, low birth weight by 49% and intrauterine growth restriction by 45%.

Although the evidence for the association between pregnancy anxiety and gestational age or preterm birth is more robust, depressed mood and chronic strain is often more consistently linked to fetal growth and low birth weight [57]. In a population-based retrospective cohort study of more than 500,000 births in California, psychiatric diagnoses predicted low birth weight after adjusting for marital status, ethnicity, and prenatal care adequacy [58]. In another study of 1,100 women screened for psychiatric disorders during pregnancy, women with a depressive disorder had significantly higher odds of giving birth to infants with low birth weight (OR = 1.82) [59]. Research on the psychological pathways contributing to low gestational age and birth weight deserve individual attention with special emphasis on the type and severity of mood disorders.

Animal models and human studies have also shown that psychosocial and physiological stressors during pregnancy are associated with long term changes in infants’ cognitive, physiologic and behavioral outcomes [60-62]. Untreated prenatal depression is the most robust predictor of postpartum depression and has serious consequences for infant and child’s development [63]. The most direct evidence comes from animal studies with prenatal exposures to physical stressors such as repeated electrical tail shock, immobilization, noise, and various forms of social stress [64-67]. In other studies using human participants, pregnant women who perceived themselves as stressed gave birth to infants with more difficult behavior, and anxious pregnant women had infants with poor attention regulation in the first year of life [68]. The offspring of women with increased levels of prenatal stress also demonstrated increased restlessness, behavioral problems, and attention regulation issues at two years of age [69]. Untreated postpartum depression leads to chronic recurrent depression and interfere with their children’s emotional, behavioral and cognitive well-being later in life [70].

A growing body of evidence indicates that depression during pregnancy is associated with risky behaviors and adverse health practices, such as poor nutrition, delayed prenatal care, adherence to medical recommendations, use of alcohol, cigarettes, and illicit substances which may lead to adverse birth outcomes [58,71-73]. The concomitant effects of depression and stress can influence lifestyle behaviors such as prenatal smoking and cessation behaviors [74]. In fact, one study showed that among pregnant women in the second trimester, smokers were significantly more likely to report depressive symptoms than never-smokers [75]. These lifestyle behaviors could account for a large portion of the risk for adverse birth outcomes. Grote et al. observed smoking had a dose-dependent relationship with preterm birth where smoking more than 10 cigarettes a day increased the likelihood of a early preterm birth of 33-36 weeks by 40 percent and of preterm birth at 32 weeks or less by 60% [56]. In addition, the magnitude of risk for preterm birth and low birth weight posed by antenatal depression was comparable to the risk of smoking 10 or more cigarettes a day. The pharmacological properties of nicotine may serve as a coping strategy for dealing with negative affect among women [76]. Women with psychosocial problems such as depression may be less confident in their changes of successful smoking cessation. Smoking may also provide a quick and direct reinforcement to depressed women with reduced capacities to initiate efforts to quit smoking [77].
4. Mechanisms of stress and preterm birth

There are multiple physiologic pathways that mediate the relationship between prenatal stress and poor birth outcomes. Primary hypothesized mechanisms for the impact of stress on preterm birth are through the neuroendocrine, inflammatory or immune, and behavioral pathways [25].

4.1. Biomedical individualism

Research on chronic stress and pregnancy gathered momentum during the 1990s at which time strong work on psychosocial, neuroendocrine, and preterm birth was generated [1]. Several prospective studies with large sample sizes and standardized measures of stress gave researchers the confidence to proceed with the understanding that stress is a risk factor for preterm delivery although the mechanisms are not fully understood [78]. In contrast, considerably less biopsychosocial research has been conducted on the mechanisms linking stress and low birth weight [3]. Nevertheless, a large proportion of work has focused on two main hypothesized biological mechanisms for preterm birth: the neuroendocrine and inflammatory pathways [78]. Though a smaller subset of preterm birth is attributed to vascular factors, the bulk of existing research has focused on the first two physiological mechanisms [3].

4.2. Physiologic stress response

Experiencing major life events, pregnancy-related anxiety, and racism or discrimination can exacerbate levels of perceived stress among individuals while higher coping skills and greater social support can be protective. While the process may vary depending on the quality (i.e. psychological or physical), strength and duration of stressors, exposure to stress can lead to two physiologic sequence of events involving the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis [1]. Figure 1 depicts the physiologic response to stress as it relates to preterm birth. Corticotrophin-releasing hormone (CRH) plays a key role in initiating and regulating the physiologic stress response. The release of CRH from the hypothalamus to the anterior pituitary initiates the systemic release of adrenocorticotropin hormone (ACTH), which signals the adrenal glands to release glucocorticoids (i.e. cortisol) [1]. Neuronal regulators of the central arousal and systemic sympathetic adrenomedullary systems are innervated to release norepinephrine from a network of neurons throughout the brain resulting in enhanced arousal and increased anxiety [79]. Activation of the autonomic nervous system and HPA axis results in physiologic and behavioral changes characteristic of “fight or flight” responses [80]. The secretion of CRH is down-regulated through a negative feedback loop where increased cortisol levels signal the hypothalamus to reduce further CRH release. Acute or short-term stress prompts the successful return to homeostasis. Long-term activation may indicate the chronic nature of stress or the body’s inability to effectively respond to stressors. It has been suggested that constant exposure to stress has cumulative effects of “wear and tear” on the body and this concept of “allostatic load” places individuals at risk for adverse health outcomes such as preterm birth [32,81,82].
4.3. Neuroendocrine

Pregnancy involves significant changes to neuroendocrine, immune, and vascular functioning that affects the uterine environment for fetal development and parturition [83]. In fact, it has been reported that up to 25 percent of preterm births are attributable to the influence of stress on neuroendocrine mechanisms [3]. As described earlier, there are two principal components of the stress response system, the CRH-releasing HPA axis and autonomic nervous system (locus ceruleus-norepinephrine system or LC/NE) [84]. Under stress, the principal regulators of the HPA axis, or CRH and arginine-vasopressin (AVP), are released by the hypothalamus into the hypophyseal portal system leading to the secretion of ACTH by the pituitary. CRH is the most potent agonist for the secretion of ACTH and beta-endorphin from the anterior pituitary. However, in the presence of stress, ACTH can also be regulated by other peptides such as AVP, oxytocin, and vasoactive intestinal peptide [78]. ACTH is transported to the adrenal gland where it stimulates both the synthesis and secretion of glucocorticoids, aldosterone and adrenal androgens [78]. It is interesting to note that there has been growing interest in observed racial and ethnic differences for CRH and ACTH during pregnancy although the mechanisms and reasons for the differences are not well understood [78,85,86].

Circulating levels of CRH-binding protein decrease substantially towards the end of pregnancy resulting in increased levels of plasma CRH [87]. During pregnancy and immediately following birth, maternal hypothalamic CRH secretion is suppressed due to the levels of circulating cortisol; thus, increasing levels of stress-induced CRH may interfere with the hormonal balance [88]. Process variations that underlie fetal growth have an influence on maternal physiologic changes, which in turn, moderate the effect of maternal stress exposure on the developing fetus. This bidirectional relationship between mother and fetus is dynamic and repetitive during pregnancy [89]. Placental CRH plays an important role in preparing for uterine growth and perfusion by communicating between the placenta and adrenal gland to release cortisol into maternal and fetal circulation [78]. In late gestation, cortisol produced by the fetal adrenal cortex blocks the inhibitory effects of progesterone on placental CRH production and leads to a surge in CRH in the placenta [90]. Placental CRH passes directly into the fetus and helps stimulate the fetal adrenal gland directly to increase dehydroepiandrosterone, a precursor for placental estrogen production [91,92]. The conversion to estrogen subsequently affects gap junction formation and oxytocin receptor expression by the myometrium and prostaglandin production that are important events for facilitating uterine contraction and labor [90]. In the presence of chronic or sustained stress, premature or exponential release of CRH gene expression in the placenta may lead to altered physiology of parturition which produces uterine contractions and result in early delivery [93]. This has served as the basis for the placental clock theory under which gene expression and over-production of CRH in the placenta affects gestational length [94]. In addition to prematurity, abnormalities in placental CRH secretion due to stress may be involved in the pathogenesis of fetal growth retardation and preeclampsia – three leading causes of perinatal morbidity and mortality in developed countries [95].
Glucocorticoids exert a broad range of effects throughout the body, one of which is to inhibit the activation, proliferation, and function of cells involved in immune response [96-98]. Short-term stress prompts the successful return to homeostasis while chronic stimulation of the HPA axis results in hypercortisolemia. Hypercortisolemia is associated with the suppression of growth and sex hormones, a diminished feedback loop, increased risk for a coronary heart disease event, insulin resistance, and obesity [99-102]. In a review of the literature on preterm birth, neuroendocrine markers, and psychosocial factors, Latendresse found that women who had higher plasma concentrations of CRH, ACTH, and cortisol, higher perceived stress or anxiety scores, more risky behaviors like smoking, and lower education were at increased risk for preterm birth [1]. Further, African-American women had higher levels of CRH and were more likely to have preterm infants. In fact, perceived stress and elevated CRH accounted for 20% of the variance in gestational age at birth [103].

4.4. Inflammatory/immune system

Maternal and placental hormones also play a role in the inflammatory pathway [87]. It has been reported that repeated episodes of stress can induce a chronic inflammatory process which is associated with inflammatory-related diseases such as atherosclerosis [104]. Inflammation is characterized by an increased production of pro-inflammatory cytokines in response to threats to tissue. The events that regulate homeostasis of the immune system and protective


Preterm Birth


[99] Rozanski, A, Blumenthal, J. A, Davidson, K. W, Saab, P. G, & Kubzansky, L. The epidemiology, pathophysiology, and management of psychosocial risk factors in


