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Chapter 2

Preterm Birth and Stressful Life Events

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Additional information is available at the end of the chapter

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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].

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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

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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

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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].

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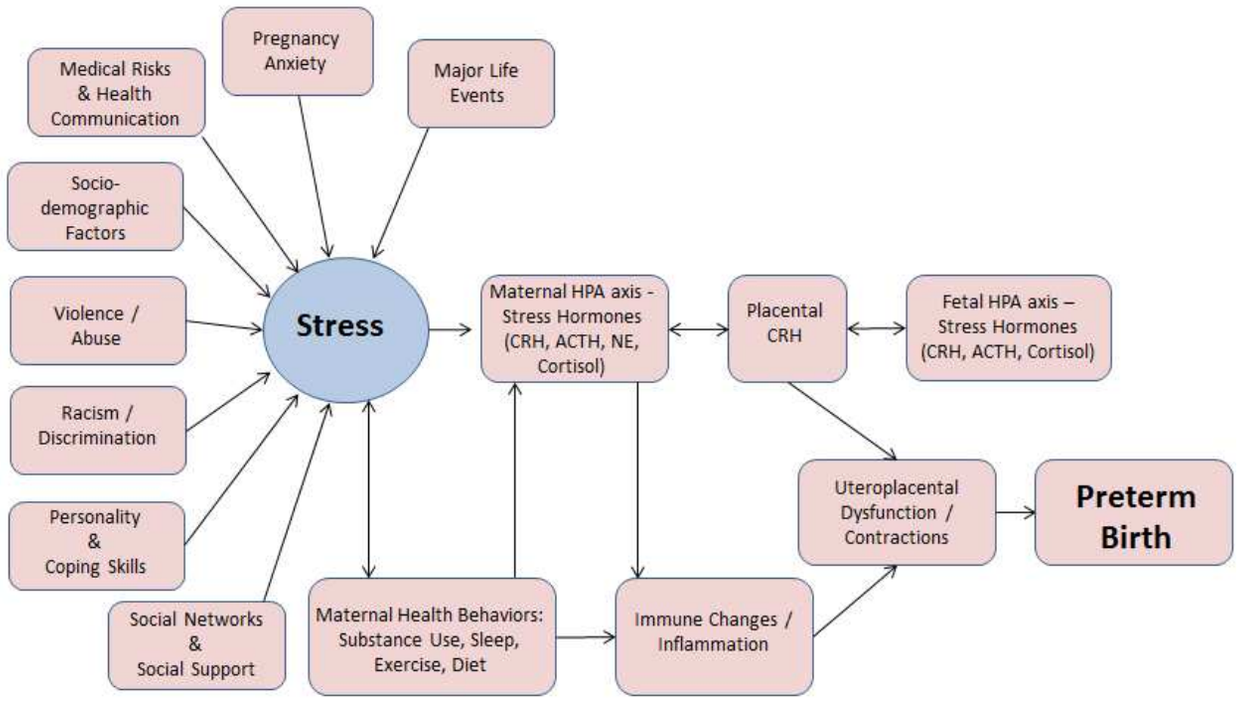
4.3. Neuroendocrine

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 exerts 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. Hypercorisolemia 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].



Modified from Dunkel Schetter [3]

Figure 1. Physiologic Stress Response in Relation to Preterm Birth

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

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response are coordinated to a large extent by cytokines regulated through type 1 and 2 helper T cells (Th1 and Th2, respectively) [105].

The immune response and inflammation that takes place during the process of fetal implantation is primarily a Th1 response with the secretion of tumor necrosis factor (TNF-β), interferon-gamma (◎-IFN), and interleukins (IL-2) [78]. Since pregnant women only share half of the fetal major histocompatibility complex (MHC) antigens, a certain degree of immunosuppression is required to keep the fetus in the uterus [105]. If the Th1 immune response persisted beyond early implantation, the pregnancy could not be viable. Thus, the immune system cedes to Th2 with a different set of cytokines (i.e. IL-4, IL-10, IL-13) that prevents rejection of fetal implantation by suppressing Th1 and promoting humoral immunity [78]. If this system or balance of cytokines was disrupted, this could lead to an abnormally high production of Th1 pro-inflammatory cytokines (e.g. TNF-α, ◎-IFN) resulting in spontaneous abortion and fetal death. Cytokines produced by Th1 destroys vascular endothelial cells which leaves the embryo vulnerable to ischemic death by increased pro-coagulant secretion [106-108].

Various factors have been known to promote a shift of the pregnancy-protective Th2 cytokine towards a Th1 response resulting in fetal death. For instance, endotoxin is a potent abortogenic substance that stimulates microphages to release cytokines in mice [109]. In addition, the exposure of pregnant mice to a stressor during the implantation period has been known to activate T cells, mast cells, and macrophages in the uterus, resulting in increased secretions of TNF-α [110]. Both pregnancy and stress share a common effect on the immune system – the switch from Th1 to Th2 immunity. Further research is needed to understand the interaction between the two systems to cause disease and elucidate why some people may be more susceptible to adverse birth outcomes or infections.

A psychosocial stress-induced release of glucocorticoids and catecholamines may cause excessive immune response through an exaggerated Th2 response and suppressed Th1 resulting in a greater risk of infection during pregnancy [78]. Reproductive and urinary tract infections, sexually transmitted diseases, and periodontal disease can pose serious risk for preterm birth. For medically indicated causes of preterm birth, stress mediates the promotion of preeclampsia which is also associated with high levels of circulating inflammatory markers [19]. A large proportion of preterm births have been attributed to the inflammatory pathway [111]. Further, high levels of chronic stress have been linked to vaginal bacterial infections at an individual and community level [128]. One must consider the role of genetics in the stress-immune interaction. However, there are no clear or definitive studies that elucidate how the effects of prenatal stress on birth outcomes may be partially mediated by inflammatory processes [3].

5. Fetal programming and life course perspective

Preterm birth is a multifaceted difficult problem and a growing body of work highlights the need for a paradigm shift in considering the interplay of biological, behavioral, psychological,

and social factors on improving birth outcomes. The life course perspective may be a useful way to think about maternal stress and preterm birth. This conceptualizes reproductive and birth problems as a result of the culminating experiences and exposures during the life course of the mother [82]. In other words, factors occurring throughout a woman's developmental lifetime, not just during the perinatal period, can alter the quality of the intrauterine environment for her offspring and have a lasting impact on their health. Research in this area has begun to shed light on possible mechanisms through which longitudinal factors produce adverse birth outcomes, such as preterm birth. Two broad mechanisms have been proposed – early programming and cumulative pathway [82].

The early programming model suggests that exposures or experiences (i.e. stressful life events) that occur at a critical period in the developmental process can alter the structure or functioning of an organism or system that becomes manifest in health and risk of disease later in life [82]. Although the biological underpinning for this model is not fully understood, some have attributed this phenomenon to poor fetal nutrition. This notion forms the basis for the Developmental Origins of Adult Disease Hypothesis or Barker's Hypothesis where under-nutrition during gestation increases risk for adult onset diseases [129-131]. Earlier animal models have indicated a critical or sensitive period in early life for the effect of altered fetal nutrition on metabolism, growth, neurodevelopment and major disease [132-136]. Although there are no studies that clearly support programming of reproductive potential, one study came close to relating maternal intrauterine environment to future reproductive outcomes. Lumey et al. found that women exposed in utero to a war-induced famine during the first and second trimesters gave birth to the lowest birth weight infants compared to women who were exposed in utero during the third trimester [137]. Human studies on birth outcomes and cardiovascular disease have also demonstrated that an adverse intrauterine environment can have long-term effects on fetal development and lead to its increased risk for adult-onset chronic disease such as diabetes and hypertension [138,139].

Research indicates a relationship between maternal stress during pregnancy and subsequent cognitive, emotional, and behavioral problems in offspring possibly through the hypothalamic pituitary axes [140-145]. It has been suggested that the association of stress and preterm birth may be mediated by epigenetic changes in the glucocorticoid receptor gene in the developing brain [146]. Perinatal stress is associated with HPA axis hyperreactivity and may be due to feedback resistance as a result of decreased expression of glucocorticoid receptors [147-149]. Mizoguchi et al. observed stress-induced attenuated glucocorticoid negative feedback among animals undergoing chronic stress. Maternal affective disorders have been known to alter fetal HPA axis and physiology [149,150].

As researchers continue to study preterm birth and the role of stress at earlier points in pregnancy or during childhood, this can help elucidate the extent to which maternal stress affects fetal growth and development. For example, in a study by Field et al. on pregnancy anxiety and neonatal behavior, newborns to high anxiety mothers showed more state changes and poor performance on the Brazelton Neonatal Behavior Assessment Scale, which evaluates motor maturity, autonomic stability, and withdrawal [151].

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Further, high anxiety mothers had significantly increased prenatal norepinephrine and lower dopamine levels than low anxiety mothers. Further studies have reported that prenatal stress is related to offspring temperament, later behavioral and emotional problems, and worse attention and concentration [68,140,152]. These suggest that maternal stress and affective state can have a significant impact on fetal neuro-development and persist throughout the lifespan of the child [124]. In addition, it shows that fetal brain functioning can be altered by measured maternal neuroendocrine dysregulation which has clinical implications when considering effective interventions to improve health outcomes.

The cumulative pathway model hypothesizes that constant exposure to stress has cumulative effects of "wear and tear" on the body's regulatory process, and this concept of "allostatic load" places individuals at risk for adverse health outcomes such as preterm birth [32,81]. There is still much to be learned on the process of cellular aging and how stress can accelerate the process. However in a landmark study that assessed psychological stress and a proxy for measuring age, Epel et al. found that an accelerated chromosomal telomere shortening was associated with higher levels of perceived stress in premenopausal women caring for their chronically ill children [153]. Telomeres are DNA-protein complexes that cap chromosomal ends and promote stability. Women with the highest level of perceived stress had shorter telomere lengths that were equivalent to aging ten years compared to women with low stress. Further, both perceived stress and long-term exposure to stress was significantly associated with higher oxidative stress and lower telomerase activity. This suggests that chronic stress contributes to increasing allostatic load, resulting in rapid cellular aging and subsequent risk of dysfunction and disease typically associated with older age. The identification of such markers within the context of pregnancy, and in relation to preterm birth could be illuminating.

Chronic and repeated exposure to stress has also been linked to immune-inflammatory dysregulation, insulin resistance, and obesity [99-102]. Suppressed immune system could increase the likelihood of genital tract infections at conception and early pregnancy. Failure to treat pathogens by mid-gestation can lead to preterm labor or premature rupture of membrane [111]. Similarly, overexposure to high levels of glucocorticoids can also lead to exaggerated hyperactive HPA response to stressors which may reflect the inability of the HPA axis to self-regulate [112,113]. Women who experience stress may yield a higher output of norepinephrine and cortisol which could increase CRH gene expression and subsequently lead to preterm birth. These two mechanisms - HPA hyperactivity and immune-inflammatory system – increase the risk for developing cardiovascular diseases, cancers, and experiencing adverse reproductive outcomes.

Several studies relate health disparities in the U.S. to the cumulative differential exposures to damaging physical and social environments [82]. This is evident in studies where preterm birth is a proxy for early health deterioration or "weathering" by age, abuse and trauma, income and poverty [114-116]. For example, Love et al. explored the transgenerational effects of poverty on preterm birth, low birth weight and small for gestational age [116]. Authors found that the age for African-American women to experience the lowest birth weight was less than 20 years which deteriorated with increasing age groups compared to White women whose lowest rate of low birth weight was in their late 20s. The degree of weathering for African

American women, with regards to low birth weight, small for gestational age, and preterm birth, depended on the duration of exposure to low-income neighborhoods and disappeared for those living in non-poor areas. In contrast, no group of white women exhibited weathering even while living in poorer neighborhoods. The biological mechanisms by which a lifetime of differential exposures to discrimination, social inequities and poverty leading to health disparities is not well understood. However, the life course perspective theory frames the issues in such a way that vulnerability to preterm birth or low birth weight is not restricted by time or space, but is all-encompassing, considering the full range of biological, psychological, financial, behavioral and interpersonal stressors and exposures that have become manifested in the widening gap between racial and ethnic groups on many health indicators.

6. Factors that influence stress

There are a multitude of factors that can affect an individual's stress level, including socio-demographic characteristics and environmental and social influences. Stress levels can vary depending on gender, race, life-events, and resiliency. Currently, stress research is fragmented into two mutually exclusive categories – childhood stress and adult or adolescent stress – failing to fully explore the potential connectivity between them. Studies have reported striking evidence on the influence of childhood stressors on neuro-endocrine systems and mental health disorders later in life [117-122]. A recent study by Danese et al. suggested that children exposed to adverse life events, exhibited psychological and physiological abnormalities as adults [123]. This is further documented by DiPietro who reviewed the role of prenatal influences on child neurodevelopment [124]. In addition, Kingston et al. linked childhood stress with prenatal stress which has a significant impact on poor birth outcomes, particularly preterm births [125]. This suggests the significance of a life course pathway to prenatal stress, which in fact includes childhood and adulthood socioeconomic positioning. Furthermore, it alludes to the recent movement in understanding the impact of maternal stress and designing interventions to address the issue of preterm births using the life course perspective [82]. The life course perspective is grounded in the theory that reproductive and poor birth outcomes are the result of the culminating experiences and exposures to stressful assaults during the life course of the mother. The mechanism for this theory is further discussed in the previous section on "Fetal programming and life course perspective".

Although the life course perspective calls for understanding of stress through the life of a prospective mother starting in utero, studies that examine these influences through the developmental stages are lacking. Existing literature predominantly focus on stress during pregnancy and its impact on poor birth outcomes. Various sources have estimated between 25 to 75 percent of women experience stressful life events or social health issues during the antenatal period [20,126]. It has also been reported that about 18 percent of women experience three or more stressful life events during pregnancy [20]. Previous studies have shown that maternal psychosocial stress is associated to education, personality traits, demographic characteristics, and environmental and social influences [2]. Research conducted outside the U.S. reports similar risk factors for stress with regards to age, parity, and prenatal care

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adequacy [20,127]. Demographic factors such as age, marital discords, intimate partner violence, low education and income are some factors that predispose women to certain levels of stress. Furthermore, stressful life events such as extreme financial distress, death in the family, accidents, injuries, persistent discrimination and other mishaps pose major stress. In fact, most of the psychometric assessments that are validated to measure stress are based on enumerating the occurrence of these life events.

6.1. Lifestyle factors

Stress is known to influence lifestyle behaviors such as smoking, alcohol use, illicit substance use, physical activity and diet. These are also known risk factors for preterm births and relatively amenable to intervention. One of the main preventable causes of preterm births is smoking. Unfortunately, the number of stressful events is inversely associated with smoking cessation. In fact, women reporting three or more stressful events are half as likely to quit smoking compared to women who report no stressful events in the previous year [74]. Smokers during pregnancy tend to be single, of low income, less education and other factors associated with smoking include physical and sexual abuse and high stress levels [154,155]. It has been proposed that since nicotine a vasoconstrictor, reduces the flow of nutrients and oxygen to the developing fetus, this may result in low birth weight infants, reductions in body length and head size, and other perinatal complications [156]. Smokers tend to have less weight gain during pregnancy and in fact, inadequate maternal weight gain has previously been associated with spontaneous preterm delivery and low birth weight infants [157].

High psychosocial stress has also been linked to use of substance, drugs, and alcohol [155,158]. There is considerable evidence on the significant association between acute and chronic stress and substance abuse [159]. It is postulated that people abuse substance and excessively drink alcohol as a means of coping with stressful situations, such as economic stress, marital discourse, and often when there is lack of social support [159-161]. However, the tendency to abuse substances when distressed depends on many factors. Some of the known factors include the intensity and type of stressor, perceived ability to overcome the stressful situation, availability of social support, genetic determinants, and prior history of substance use. Several theories were proposed to understand the role of stress in substance abuse and particularly addiction process. The most frequently cited mechanism was the psychological response to substance abuse that postulates substance abuse or use as a means to cope with stress and in most cases to simply alleviate tension [162-168]. The neurobiological model is another theory that proposes the mechanism for addition. This theory emphasizes the role of incentive sensitization and stress allostasis and provides explanation for craving and loss of control [159,169].

7. Social production of disease/political economy of health

Health disparities among racial and ethnic groups are influenced by the structural, institutional, and interpersonal aspects of society and its health care systems [170]. Stemming from

the social analyses of health from the 1830s and emerging in the politically turbulent 1960s and 1970s, this theoretical framework focuses on the "social production of disease" and/or "political economy of health" [171-173]. That is, it addresses economic and political determinants of health and disease and any structural barriers that prevent people from living healthier lives [171-179]. The underlying principle is that economic and political institutions that create, enforce, and perpetuate economic and social privilege and inequality are causes of inequities in health which are also stressors in life [179,180].

Going beyond just healthy choices and behaviors at an individual level, this school of thought takes into consideration significant external forces that perpetuate the disparities in health evident in different populations around the world. For example, disquieting health disparities between Australia's indigenous Aboriginals and the rest of the population has been observed in higher infant mortality rate, more drug abuse and alcoholism, chronic and infectious diseases, and poverty [181]. The average Aboriginal household earns only half of what a typical Australian family earns in a week and poverty has been associated with social problems to varying degrees such as high imprisonment and unemployment rates [182].

Like gender and race, religion forms part of the context that generates stress-inducing social inequities and may influence people's socioeconomic status and health outcomes. Of the 1.6 million Muslims living in the UK, 74% were of Asian ethnic background with smaller proportions of black African Muslims and white British in 2001 [181]. In the US, an estimated 6 to 7 million Muslims is comprised of South Asians (32%), Arabs (26%), and African-Americans (20%) [182]. One study that used aggregate data from 10 different data sources (i.e. World Health Organization, United Nations, UNICEF) indicated significant health disparities between countries with a Muslim majority and non-Muslim majority [184]. National health indicators such as male and female life expectancies, maternal mortality ratio, and infant mortality rate were worse in Muslim majority countries compared to non-Muslim majority countries. Almost half of non-Muslim majority countries were in the high or upper middle income group compared with a quarter of all Muslim majority countries. In fact, annual per capital expenditure on health in Muslim majority countries was a fifth of that in non-Muslim majority countries. Additionally, gross national income, literacy rate, access to clean water, and government corruption accounted for 52 to 72 percent of the differences in health outcomes between the two groups. The gradient in health within and between countries can be linked to the unequal distribution of power, income and goods or services. The structural determinants and conditions of daily life make up the social determinants of health, and can account for a large portion of the health inequities observed within and between countries [184].

Discrimination and poverty pose serious challenges in closing the health gaps between racial and ethnic groups. Following the fall of Apartheid South African's Government of National Unity defined and proposed five key developmental priorities to work towards rebuilding the community: employment, housing, education, nutrition, and health [185]. Nearly two decades later, racial and economic discrimination undermine the progress and development in achieving these goals. Racial group still appear to be a strong determinant of income, education, health care coverage, and the quality of medical treatment [186,187]. Similarly, using data from a national survey, Charasse et al. reported that even after controlling for important socio-

demographic characteristics, Whites and Africans did not share the same level of health risks [185]. Authors found that Whites tended to have higher income, better education, and more favorable health status than Africans.

A large population-based survey of newly mothers in Australia also highlight a concerning level of social adversity associated with stressful life events and social health problems during pregnancy [20]. One in six women reported experienced three or more stressful life events or social health issues in the 12 months preceding the birth. Women who experienced more life events and social health problems were significantly more likely to report discrimination in the health care settings (OR = 2.69, 95% CI = 2.2 to 3.3) and had a twofold increased odds of having a low birth weight infant compared with women reporting no social health issues. They were also more likely to have antenatal care later in pregnancy and with fewer visits.

Over the past 50 years, improved and expanded prenatal care has resulted in the identification of high-risk pregnancies, leading to an overall reduction of infant mortality in the United States. In the early 1900s, 100 infants died for every 1,000 live births before reaching their first birthday [188]. Since then, the infant mortality rate has declined by more than 90 percent to a rate of 7.2 deaths per 1,000 live births in 2000 [189]. However, African-Americans have been disproportionately affected by the problem. Preliminary results from the U.S. Centers for Disease Control and Prevention showed that the mortality rate for black infants was 11.6 deaths per 1,000 live births compared with 5.2 deaths per 1,000 live births among white infants [190]. In short, black infants die at 2.2 times the rate of white infants within the first year of life. Even after controlling for socio-demographic factors, African Americans with adequate prenatal care still have poorer birth outcomes than their White counterparts [188].

In the U.S., African American women are more likely to die from pregnancy-related complications, have preterm or low birth weight infants, deliver an infant with congenital anomalies, experience a spontaneous abortion and ectopic pregnancy compared to women of other racial and ethnic backgrounds [191-196]. The influence of income on adverse pregnancy outcomes has been previously examined in military populations where pregnant women do not necessarily have financial barriers to health care. Although black women in the military have better pregnancy outcomes than black women in the general population, disparities persist between black and white enlisted women [197]. Furthermore, disparate birth outcomes are evident even among those who are college-educated. Although education is known to be a protective factor against adverse birth outcomes, black women with higher education experience disproportionately high rates of low birth weight compared to college-educated white women [198]. These disparities underscore the need to consider factors other than socioeconomic status to account for the health disparities.

Speculations that racial disparities in adverse health outcomes is attributable to genetic factors have been contradicted by studies that found black immigrants from African or Caribbean do not experience the same rates of adverse pregnancy outcomes as African-Americans from the U.S., in fact, they begin to show worse health outcomes the longer they live in the U.S. [199-201] Racial disparities in adverse outcomes has spurred interest in the role of psychosocial

factors such as stress in pregnancy [202]. It has been previously documented that African American women report a greater number of life events and are more distressed by them than any other racial or ethnic groups [25,203]. Racism can be conceptualized as an individual-level psychosocial stressor and is defined as a multidimensional construct that involves the oppression and denigration of individuals by other individuals and social institutions on the basis of skin color or membership in a particular ethnic group [204].

Perceived racism across the lifetime is a significant predictor of birth weight in African Americans and may account for racial differences in infant mortality rates [205]. Preterm birth is also suggested to occur in the context of social and economic structures such as acculturation stress, racism, and poverty [2]. For example, a small prospective observational study was conducted to examine the roles that general, pregnancy, and racism stress play in racial differences in birth outcomes (birth weight and gestational age) [205]. Perceived racism and indicators of general stress were associated with low birth weight. Lifetime and childhood indicators of perceived racism predicted birth weight and attenuated racial differences independent of medical and socio-demographic variables.

The stress of perceived racism and discrimination, differences in how the health care system responds to individuals of different racial backgrounds should be further evaluated to address the slow progress in closing the large health gap between racial and ethnic groups. While it is important to acknowledge the role of individual factors such as discrimination and racism on prematurity and low birth weight, this problem is multifaceted and should compel policy-makers, social services, and health care providers to recognize all the other behavioral, medical, social, environmental, and institutional factors that contribute to the persistent racial and ethnic health disparities. Efforts to reduce discrimination and racism must be taken in the context of ensuring safe neighborhoods, access to healthy food, quality and culturally sensitive medical care to have high impact on such a complex problem. Intervention efforts to improve birth outcomes in the U.S. have had limited success, in part, due to a focus on individual level programs that fail to consider contexts affecting maternal and child health, including neighborhood exposures [206-208]. This necessitates support for social and health programs that provide more comprehensive care for women. Recognizing this need, programs have been designed and implemented to address some of the social determinants. For instance, The Healthy Start program is a U.S. federally-funded initiative to reduce the national infant mortality rate and improve perinatal outcomes by leveraging community resources and workers [209].

8. Measurements

In order to fully understand the role of stress on perinatal health, it is important to effectively quantify and measure its characteristics. Defining or measuring stress can be confusing due to the differences in nature and duration of exposure. Identifying the impact on high-risk populations and the correct manner in which to assess stress poses a great task for researchers. Prior research highlights the importance of differentiating between global stress and preg-

nancy-specific stress in order to better understand and identify the impact of prenatal stress on maternal and infant health outcomes [210]. Pregnancy-specific stress is defined as the emotional response to the stressfulness of pregnancy itself [210]. It has been suggested that pregnancy-specific stress may have a more deleterious impact on birth outcomes such as preterm birth [210]. Differences between the types of stress and how they contribute to poor birth outcomes has yet to be fully explored.

Previous work yield many different stress measures, however, the most commonly used instruments can be classified into four domains based on a construct published elsewhere – external, perceived, enhancers, and buffers [21]. Examples of external stressors include life events or daily hassles; perceived stress reflect perceptions of racial or gender discrimination and other subjective stress levels; enhancers of stress include anxiety or depression; and buffers of stress cover social support systems and coping mechanisms [4,21]. General stressful life events measures (e.g. General Health Questionnaire and Perceived Stress Scale and pregnancy-specific stress instruments (e.g. Pregnancy Experience Scale, Pregnancy-Related Anxiety Questionnaire, Pregnancy-Related Anxiety Scale, Pregnancy-Specific Anxiety Scale, Prenatal Distress Questionnaire, and Prenatal Social Environment Inventory) have been used throughout literature [210,211,219]. Table 1 summarizes commonly used measures for experiencing global or pregnancy-specific stress.

8.1. General Health Questionnaire (GHQ)

Originally developed by Goldberg the General Health Questionnaire (GHQ) is a widely used instrument for measuring general psychological health in community settings and non-psychiatric clinical settings such as primary care [211]. In general the GHQ focuses on two main classes of phenomena: inability to carry out one's normal healthy functions; and emergence of new phenomena that are distressing [212]. Translated into 38 different languages and available in a variety of versions using 12, 28, 30, or 60 items, this instrument demonstrates high reliability and validity in many different populations with reliability and correlation coefficients ranging from 0.78 to 0.95 [213-216] and 0.35 to 0.79 [217-218], respectively. The 12- items GHQ is one of the most extensively used screening instrument for common mental disorders [219] and its brevity makes it an attractive choice for use in busy clinical settings and for patients who need help to complete the questionnaire [220]. Responses to each item ranges from zero (not at all) to three (much more than usual) with a total possible score based on the version allowing for means and distributions to be calculated.

8.2. Perceived stress scale

The Perceived Stress Scale (PSS) is one of the most widely-used psychological instruments for measuring the perception of stress [221]. The scale includes a number of questions about the level of experienced stress over the previous month and has three versions with 14, 10, and four items, respectively. The PSS prompts subjects to rate on a scale from zero (never) to four (very often) how often they have perceived an event or negative feeling in the past month. This tool demonstrates strong internal consistency, with a Cronbach's alpha ranging from 0.75 to

0.91 [221-223]. It also has the virtues of being brief, easy to understand, and assessing stress response in the general population on a continuum from relatively mild to severe forms of stress.

Similar to other non-specific stress measures, a major limitation of GHQ and PSS is the failure to differentiate between general stress and pregnancy-specific stress. Although pregnancy-specific stress may occur concomitantly to general or non-specific stress, research suggests that pregnancy-specific stress may be particularly more potent and have serious implications on birth outcomes [34,61,68,224,225]. For example, Roesch et al. found that pregnancy anxiety predicted earlier birth while general state anxiety and general perceived stress did not [225]. The timing of prenatal stress exposure may also be of importance. In one study, researchers found that stress experienced during the second trimester was more predictive of preterm delivery than exposure to stress later in the pregnancy [27]. Several studies have shown a decline in psychological and physiological stress response in pregnant women as pregnancy progresses [28-30]. For example, Glynn et al. reported that pregnant women who experienced the 1994 Northridge earthquake in California showed a differential emotional response to 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. Considering the type of stress and time frame of maternal exposure to stress may be useful in understanding the impact on developing fetus.

Measure	Description	Number of Items	Scale Type	*Cronbach's Alpha	€Test-retest Reliability
General Health Questionnaire	Screening tool for detecting non-specific psychiatric illness through items that address the inability to perform daily activities and feelings of distress	12, 28, 30, 60	4-point	0.78 - 0.95	0.35 - 0.79
Perceived Stress Scale	Measures the degree to which situations in one's life over the past month are appraised as stressful (i.e. unpredictable, uncontrollable, and overloading)	4, 10, 14	5-point	0.75 - 0.91	0.85 (over two days)
Pregnancy Experience Scale (hassles subscale)	A measure containing two subscales of which the "hassles" subscale is intended to reflect the daily challenges related to pregnancy (frequency and intensity of hassles)	20	4-point	0.91 - 0.95	frequency 0.57 - 0.83; intensity 0.61 - 0.76

Measure	Description	Number of Items	Scale Type	*Cronbach's Alpha	€Test-retest Reliability
Pregnancy-Related Anxiety Questionnaire-Revised	Measures specific fears and worries related to pregnancy (i.e. delivery, infant health, and egocentric feelings/fear of change)	34	5-point	0.73 - 0.88	0.56 - 0.76
Pregnancy-Related Anxiety Scale	Items assess the extent to which participants worry or feel concerned about their health, baby's health, labor and delivery, and postpartum infant care	10	4-point	0.70 - 0.85	0.83
Pregnancy-Specific Anxiety Scale	Includes pregnancy-specific anxiety items that addresses maternal affective states during pregnancy	4	5-point	0.51 – 0.72	0.56 - 0.68
Prenatal Distress Questionnaire	Evaluates the most common concerns of pregnant women relating to birth and baby, weight and body image, and emotions and relationships	12	5-point	0.80 - 0.81	0.75
Prenatal Social Environment Inventory	Items cover potential stressors over the past 12 months associated with family and marital relationships, health, pregnancy, work, neighborhood, parenting, and finances	41	Yes/No	0.80	0.73

* Cronbach's alpha (internal consistency reliability) is a measure of inter-item correlations

€ Test-retest reliability (correlation coefficient) is a measure of stability over time

Table 1. Commonly used general and pregnancy-specific stress measures

8.3. Pregnancy Experience Scale (PES)

The PES [226] was developed in 1999 to evaluate maternal appraisal of positive and negative stressors during pregnancy, with reliability and validity data reported within later studies [61,224,227]. The scale aimed to reflect the daily minor challenges and positive emotions experienced by pregnant women. The scale consists of 41 items of which 20 are in the hassles subscale. Questions on discomforts of pregnancy, body changes, relationships, and concerns about the infant are among the topics specific to pregnancy-related stress. Respondents are directed to indicate whether each item is a hassle and/or an uplift on a four-point Likert scale, ranging from zero (not at all) to three (a great deal). In addition to calculating the frequency

and intensity of hassles and uplifts scores, a composite ratio score of positive to negative experiences in pregnancy can be ascertained with values greater than one indicating more hassles and scores lower than one indicating more uplifts than hassles. The alpha internal reliability rating ranges between 0.91 and 0.95 [212]. Authors wanted to challenge research that focused too narrowly on just the distressing aspects of pregnancy by also considering the role of positive emotions in fostering good pregnancy outcomes.

8.4. Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R)

The Pregnancy-Related Anxiety Questionnaire was a 55 item measure developed by Van den Bergh in 1990 that addressed common pregnancy fears (e.g. fear for delivery and baby's health) which led to a shorter version (PRAQ-R) that later became available in 2002 [68,228]. PRAQ-R consists of 34 items with responses to questions on a five point scale ranging from "never" to "very often". PRAQ-R presents good internal consistency and convergent validity data with general stress or anxiety measures. Further analysis of PRAQ-R shows a test-retest reliability rating of 0.56-0.76 and a range in alpha internal reliability rating of 0.73-0.88 [68,152]. No predictive validity data related to preterm birth has been reported to date. Given that PRAQ and PRAQ-R were designed using low-risk populations in Belgium and Netherlands, the applicability to other more diverse communities may be limited.

8.5. Pregnancy-Related Anxiety Scale (PRAS)

Rini et al. revised the PRAS with the goal of linking psychological stress and birth outcome [34,229]. The revised PRAS was used to assess the association between prenatal psychosocial stress, personal resources, sociocultural context, and infant birth weight and gestational age at birth. This was done by having respondents complete a ten item scale assessing their level of stress surrounding various pregnancy related situations; responses were on a four-point Likert scale, ranging from never or not at all, to a lot of the time or very much. There is no recall period for the PRAS because it asks how the respondent is feeling at present time. The internal reliability of the revised version of PRAS in English and Spanish ranged from 0.70 to 0.85 [210, 229]. One aspect of the PRAS that is seldom seen in stress measures is the stress surrounding the mother's thoughts regarding her pregnancy. Stress generated by a mother's thoughts about the pregnancy and birth is an important component in maternal stress research.

8.6. Pregnancy-Specific Anxiety Scale (PSAS)

Developed at the University of California, Los Angeles, the Pregnancy-Specific Anxiety Scale (PSAS) is composed of four pregnancy-specific anxiety items derived from a factor analysis of a larger pool of items that addressed maternal affective states during pregnancy [225]. In the first study that reported using PSAS to find associations with gestational age, participants were encouraged to talk about how they felt about being pregnant and asked to indicate how often they felt anxious, concerned, afraid or panicky in the previous week. All responses were provided on a 5-point scale ranging from one (not at all) to five (very much). It was determined that pregnancy-specific anxiety was associated with shorter gestation age after controlling for

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known risk factors. Further analysis of PSAS in Canada and in the U.S. shows a test-retest reliability rating of 0.56-0.68 and a range in alpha internal reliability rating of 0.51-0.72 [225,230-232]. Poor internal consistency, lack of correlation to physiological measures of stress, and failure to replicate findings in African-American populations are noteworthy limitations.

8.7. Prenatal Distress Questionnaire (PDQ)

Originally reported by Yali and Lobel in 1999, the 12-item Prenatal Distress Questionnaire (PDQ) was created and tested in a pilot to create pregnancy-specific distress scores [126]. Participants were asked to indicate how concerned or worried they were about their pregnancy on a five-point scale ranging from zero (not at all) to four (extremely). Questions pertained to three main types of concerns: birth and baby, weight and body image, and emotions and relationships [235]. Responses were then summed to create a total pregnancy-specific distress score for each individual. Several studies from the US, Germany and UK have provided reliability and validity data on the instrument. With an alpha internal reliability rating range of 0.80 - 0.81 and a test-retest reliability rating of 0.75, the PDQ demonstrates good internal consistency [127,234-236].

8.8. Prenatal Social Environment Inventory (PSEI)

In 1992, Suezanne Orr and her colleagues developed the PSEI to address limitations from the use of other life events inventories [237]. Such drawbacks were the inclusion of items that would prove to be inapplicable to certain subgroups, as well as assessing chronic stressors with the use of lengthy instruments, or instruments that are not germane to some subgroups. The PSEI consists of 41, yes or no questions, assessing stress in the past year. The 30-day test-retest reliability rating was 0.73 and the alpha internal reliability rating was 0.80. While the PSEI samples a wide variety of potential stressors, the range of information obtained with its yes or no response, is limited. In essence, the PSEI is a good measure of the prevalence of potentially stressful events in the past year, but lacks the ability to obtain qualitative data on the effects of those stressful events on the respondent.

Although some pregnancy-specific stress measures are able to predict adverse outcomes, the theoretical underpinnings of measures are lacking and largely undocumented in the literature [210]. Further consideration of theoretical models in stress measurement development can help build confidence in the use of pregnancy-specific stress measures for studies and lead to more effective stress reduction interventions that target specific concerns and groups of women rather than global and untailored interventions. Furthermore, inconsistent use of measures and definitions to assess stress has been a challenge in accurately understanding its health consequences. While interviews are useful for minimizing missing data by connecting with study participants, stress is often assessed by asking an individual to recall events that have occurred in either the distant or recent past. This introduces recall bias and compromises the reliability of the measure. Questionnaires and interviews are also subjective means to ascertain stress that may be prone to recall bias. However, the possibility of bias should not be grounds for rejection of a stress measure, rather, it should be considered in any conclusions drawn from the data.

Scientific advancements have uncovered possible biological markers (or biomarkers) of stress that provide objective and quantifiable measures, and solutions to the difficulties of qualitatively measuring stress. Biomarkers are defined by Hulk et al. as "cellular, biochemical or molecular alterations…in biological media such as human tissues, cells, or fluids" [238]. These biomarkers that are obtained from saliva, urine, and plasma may provide an objective measure for understanding the cause, progression, and worsening of maternal stress [239]. For example, maternal levels of cortisol, C-reactive protein, and alpha-amylase have been identified as markers for stress and possible biological mechanisms associated with the increased risk for pregnancy complications and preterm birth [240-242]. These markers include the use of technologies that expand people's understanding on the underlying pathogenesis of preterm birth and risk factors [243]. In epidemiologic or medical research, biomarkers address the need for more direct measurement of exposures in the causal pathway of disease that is free from recall bias and improved validity [244].

9. Conclusion

Stress is an important risk factor affecting preterm birth. Despite the growing literature, there are gaps that need to be addressed. Definitive studies that link stress, inflammation, and preterm birth need to be further explored. Specifically, more research is needed to assess pregnancy anxiety and its mediating effects on early birth. Indeed, stress pathways may be an entry point to other vascular and inflammatory pathways leading to premature delivery and low birth weight [78]. Many studies report the deleterious effects of stress on the fetal neurodevelopmental process that may have repercussions even into childhood. Arguments for the life course perspective or social productions of disease are alternative explanations that move the discussion beyond just individual choices and behaviors. The problem is complex and requires a multifaceted approach to come to meaningful and realistic solutions. In addition, there is a need for more research in coping, resiliency and other stress management techniques during pregnancy [3]. While studies that explore the effects of stress on birth outcomes are important, more is needed to develop and test interventions or prevention programs with respect to a positive impact on birth outcomes [1]. Health care providers can be better informed to refer patients to appropriate resources and supplemental services. Social support interventions need to be guided by predictive models and more needs to be done to elucidate which components of interventions account for the largest variability in birth outcomes. Lastly, more work can be done to evaluate how physiologic responses to stressors might account for health disparities [245]. Progress in improving birth outcomes is undermined by growing health disparities between various sub-populations. This should compel policymakers and health care providers to recognize all the other behavioral, medical, social, environmental, and institutional factors that contribute to persistent racial and ethnic health disparities.

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