Published in final edited form as:

Prog Neurobiol. 2012 November ; 99(2): 106–116. doi:10.1016/j.pneurobio.2012.07.003.

Physiological Reactivity to Psychological Stress in Human Pregnancy: Current Knowledge and Future Directions

Lisa M. Christian, PhD^{a,b,c,d}

^aDepartment of Psychiatry, The Ohio State University Medical Center, Columbus, Ohio, 43210

^bThe Institute for Behavioral Medicine Research, The Ohio State University Medical Center, Columbus, Ohio 43210

^cDepartment of Psychology, The Ohio State University, Columbus, Ohio, 43210

^dDepartment of Obstetrics and Gynecology, The Ohio State University Medical Center, Columbus, Ohio, 43210

Abstract

Cardiovascular and neuroendocrine reactivity to acute stress are important predictors of health outcomes in non-pregnant populations. Greater magnitude and duration of physiological responses have been associated with increased risk of hypertensive disorders and diabetes, greater susceptibility to infectious illnesses, suppression of cell-mediated immunity as well as risk for depression and anxiety disorders. Stress reactivity during pregnancy has unique implications for maternal health, birth outcomes, and fetal development. However, as compared to the larger literature, our understanding of the predictors and consequences of exaggerated stress reactivity in pregnancy is limited. This paper reviews the current state of this literature with an emphasis on gaps in knowledge and future directions.

Keywords

pregnancy; stress; cardiovascular reactivity; neuroendocrine reactivity; physiology

1. Introduction

Cardiovascular and neuroendocrine reactivity to acute stress are important predictors of health outcomes in non-pregnant populations. Greater magnitude and duration of physiological responses have been associated with increased risk of hypertensive disorders and diabetes, greater susceptibility to infectious illnesses, suppression of cell-mediated immunity as well as risk for depression and anxiety disorders [1–7].

In pregnancy, maternal stress (i.e., perceived stress, depressive symptoms, racial discrimination, stressful life events, and pregnancy-specific anxiety) has been associated with preterm birth, low birth weight, risk of gestational hypertension, and adverse health and behavioral outcomes in offspring [8–16]. Thus, differential reactivity to daily life stressors may have unique implications in the context of pregnancy. However, as compared to the

© 2012 Elsevier Ltd. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

larger literature, our understanding of the predictors and consequences of exaggerated stress reactivity in pregnancy is limited. This paper reviews the current state of this literature with an emphasis on gaps in knowledge and future directions.

2. Stressor Exposure versus Physiological Responses: Implications for Health

The current review focuses on physiological reactivity as an individual difference which has cumulative effects over the course of the life span; that is, the magnitude and duration of physiological activation in the context of psychological challenge. Exposure to stressors is predictive of adverse perinatal outcomes in groups of women. The number and severity of major life events (e.g., divorce, death in the family, illness, loss of a job) during pregnancy has been associated with risk of preterm birth [17–19]. Similarly, exposure to chronic (e.g., homelessness) or catastrophic (e.g., earthquake, terrorist attack) events has been associated with adverse birth outcomes [20–22]. However, clearly, not all women experience adverse outcomes upon stressor exposure. The biological impact of stress is ultimately a function of stressor exposure as well as the magnitude/duration of one's physiological response. Importantly, these factors interact. The experience of chronic or repeated stressors, such as that conferred by racial minority status, may sensitize physiological stress responses. Indeed, as compared to Caucasians, African-Americans exhibit greater cardiovascular reactivity to a variety of acute stressors [23–27]. Thus, assessment of individual differences in stress reactivity in addition to assessment of frequency and severity of exposure to stressors is critical for both delineating the impact of stress on prenatal health and predicting which individuals are at greatest risk for adverse outcomes upon stressor exposure.

3. Basal Physiological Adaptation During Pregnancy

Key to stress responding, functioning of the hypothalamic-pituitary-adrenal (HPA) axis is altered dramatically during pregnancy, largely due to the influence of the placenta (Figure 1). Placental production of corticotropin-releasing hormone (CRH) increases exponentially as pregnancy progresses, with up to 1000-fold increases in plasma CRH by term [28]. There is strong evidence that plasma CRH serves as a marker of the progression of the 'placental clock' which determines the timing of delivery, with differential patterns of plasma CRH levels across pregnancy among women delivering at term, preterm, and post-term [29, 30]. Notably, placentally-derived CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity [28, 31]. The bioavailability of CRH is buffered somewhat by CRH-binding-globulin (CBG). CBG drops considerably in the days prior to parturition and is a key factor instigating labor onset.

Increases in placentally-derived CRH across pregnancy stimulate secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. This, in turn, stimulates production of cortisol from the adrenal glands, resulting in hypercortisolism. While the diurnal cortisol rhythm is generally maintained across pregnancy, both total and free plasma cortisol concentrations rise in parallel as pregnancy progresses, with plasma cortisol levels 2- to 3-fold higher than nonpregnancy by term [32]. These substantial increases in ACTH and cortisol result in gradual hypertrophy of both the pituitary and adrenal glands. Despite these pregnancy-related changes, psychosocial stress is associated with measurable effects on cortisol levels [33] and higher cortisol early in gestation has been linked to risk of spontaneous abortion [34]. Moreover, it has been suggested that placental-production of CRH is a stress-sensitive, thus influencing the timing of parturition [35, 36].

The maternal cardiovascular system also undergoes substantial changes to support fetal development during pregnancy (Figure 1). Blood volume increases by approximately 45%.

Due to increases in stroke volume and heart rate, cardiac output increases by 30–50% while systemic vascular resistance decreases. A decrease in blood pressure is seen, with a nadir at mid-gestation followed by an increase to pre-pregnancy levels by term. Lack of such adaptation has been associated with adverse outcomes. Higher blood pressure during the first trimester of pregnancy is predictive of greater risk of subsequent preeclampsia [37, 38]. Moreover, higher blood pressure has been associated with lower birth weight, even among normotensive women [39, 40]. Stress may contribute to this association. For example, in a study of 170 African-American and white women assessed longitudinally across pregnancy, stress was associated with higher systolic and diastolic blood pressure among African-Americans only [40]. In addition, an interaction between stress and blood pressure was evidenced whereby the combination of higher stress and high DBP predicted increased likelihood of low birthweight among African-Americans.

There is conflicting evidence regarding pregnancy-related changes in plasma catecholamines (i.e., epinephrine and norepinephrine); there are reports of no changes [41–43], and increasing [44, 45] or decreasing [46, 47] levels as pregnancy progresses. However, there is consistent evidence that plasma epinephrine and norepinephrine are elevated among pregnant women with preeclampsia or gestational hypertension as compared to pregnant women without these conditions [48, 49]. Further, elevations in catecholamines during pregnancy have been associated with occupational stress [50].

4. Adaptation of the Stress Response During Pregnancy

As described, successful pregnancy is characterized by substantial adaptive changes in cardiovascular and neuroendocrine parameters. Importantly, these physiological systems are *dynamic*, allowing for responses to changing environments. Studies to-date suggest that, as compared to non-pregnant women, healthy pregnant women exhibit attenuated stress reactivity in terms of cortisol, catecholamine, and blood pressure responses [51]. Similarly, dampened responsivity has been reported in rodents [52–54]. These adaptations may serve a protective function, preventing the mother and fetus from excessive exposure to stress hormones and alterations in cardiovascular parameters including uterine blood flow. Thus, individual differences in physiological adaptation during pregnancy may have consequences for maternal health, fetal development, and birth outcomes. Below, relevant literature is reviewed with an emphasis on promising applications of stress reactivity models in understanding perinatal health.

4.1. Cardiovascular Reactivity

More than one dozen studies have examined blood pressure or heart rate reactivity to acute stress among pregnant women [55–72]. In comparison to non-pregnant women, blood pressure reactivity to acute stress is attenuated among pregnant women on average. For example, compared to 34 non-pregnant controls and their own pre-pregnancy responses, 21 pregnant women exhibited lower blood pressure responses to acute psychosocial stressors including mental arithmetic [69]. Similarly, among 148 women assessed at 17 and 31 weeks gestation, heart rate and blood pressure responses to the Trier Social Stress Test (TSST) were attenuated at later compared to earlier pregnancy [72]. While an overall attenuation of cardiovascular responses among pregnant women is evidenced, there remains a great deal of variability within pregnant women as a group [51], supporting an individual differences approach in examining stress reactivity in pregnancy.

Despite the large number of studies with a focus on cardiovascular parameters in pregnancy, there is a lack of data using impedance cardiography which assesses mechanisms underlying blood pressure change. Blood pressure reflects the component processes of cardiac output (CO) and total peripheral resistance (TPR). Individuals can be classified as myocardial or

vascular responders based on their tendency to respond to stress with increased cardiac output versus vascular resistance, respectively [73]. A tendency toward vascular responding has been reported among those at greater risk for cardiovascular diseases, including Blacks compared to Whites [74] and high hostile compared to low-hostile adults [75]. Vascular responding may result in detrimental health effects in several ways, including slower habituation to stress and promotion of endothelial dysfunction [76]. Thus, frequent or extended peripheral vasoconstriction may lead to increases in resting peripheral resistance over time, resulting in hypertension [76].

As described, healthy pregnancy is characterized by decreases in vascular resistance and increases in stroke volume as pregnancy progresses; thus, a tendency towards vascular responding may have unique implications during pregnancy. Importantly, differential hemodynamic response patterns may be evidenced even when overall blood pressure responses are equivalent [77]. Therefore, utilization of impedance cardiography methodology could provide highly novel information regarding physiological adaptation during pregnancy, allowing for insight into mechanisms by which altered blood pressure may affect fetal development and birth outcomes. Indeed, available studies demonstrating associations between blood pressure or blood pressure reactivity with birth outcomes have been unable to ascertain if these effects represent a causal relationship or if blood pressure changes simply correspond to other parameters such as neuroendocrine functioning [e.g., 40, 68]. Examination of the mechanisms underlying blood pressure change will help to clarify the extent to which cardiovascular factors play a direct causal role in adverse outcomes.

Heart rate variability (HRV) represents another important avenue for future research. A simple but powerful measure of autonomic control of the heart, HRV is a measure of cyclical variations in beat-to-beat intervals. Low vagal tone, as indicated by low HRV, has been associated with impaired cardiovascular, endocrine, and immune (i.e., inflammatory marker) recovery following acute stress [78]. In relation to health outcomes, low HRV is associated with many pathological conditions and predicts risk for all-cause mortality in the elderly [79], risk for cardiac events in the general population [80] and poor prognosis in patients with heart disease [81]. In addition, diminished HRV has been recognized as an indicator of fetal distress for decades [82]. Several studies have reported a link between negative psychological factors (e.g., anxiety, hostility, depression, attachment insecurity) and low HRV or less adaptive HRV responses to acute stress in non-pregnant adults [83–85].

Corresponding to increases in resting heart rate as pregnancy progresses, heart rate variability decreases with gestational age in healthy pregnancies [86–88]. Differential changes in heart rate variability over the course of gestation have been reported among women with versus without gestational hypertension [86]. One study has examined HRV responses to acute stress in pregnancy; results showed no significant differences in HRV responses to the Trier Social Stress Test among Swiss women in the 2nd trimester or 3rd trimester compared to non-pregnant controls [89]. Overall, there are minimal data on predictors or clinical meaning of changes in basal HRV or HRV responses to stressors in pregnancy. Studies of HRV in pregnancy may greatly enhance our knowledge of effects of stress because 1) the vagus strongly affects cardiovascular functioning and is also believed to play an inhibitory role in the regulation of inflammatory processes and the HPA axis and 2) autonomic dysregulation may present well before clinical manifestations of disease, providing a useful prognostic indicator of risk [90].

4.2. Neuroendocrine Reactivity

Compared to the cardiovascular literature, fewer studies of pregnant women have examined responsivity of the hypothalamic-pituitary-adrenal (HPA) axis. However, available data

indicate that cortisol reactivity to stress is attenuated during pregnancy. For example, in response to a hand cold pressor test, 10 non-pregnant women showed significant cortisol reactivity while 10 women assessed at 37 weeks gestation exhibited no cortisol increase [57]. Similarly, down-regulation of the HPA response system has repeatedly been observed in both pregnant and lactating rats [e.g., 53, 54, 91]. Similarly, attenuated catecholamine responses have been observed in pregnant women in response to psychological and physiological stressors [e.g., 41, 67]. As with cardiovascular literature, studies to-date have focused primarily on quantifying differences between pregnant versus non-pregnant women. Attention to variability in how women adapt to pregnancy (e.g., individual differences in neuroendocrine change from nonpregnancy to pregnancy) as well as variability in absolute responses among pregnant women as a group represent the next step necessary to move this literature forward.

Of note, information about salivary or serum cortisol provides incomplete information regarding the functional effects of cortisol. Cortisol is the natural ligand for the glucocorticoid receptor (GR). Although cortisol levels are commonly measured, GR function is rarely assessed. However, GR function is a key determinant of the functional effects of cortisol; there are many steps involved in the action of GR signaling and defects in any of these steps could result in generalized or cell-specific glucocorticoid resistance [92]. Thus, assessment of glucocorticoid receptor function in future studies would better elucidate the functional effects of cortisol during pregnancy versus nonpregnancy.

Another important consideration for future research is the time of day of assessment. As described, there is a substantial increase in cortisol as pregnancy progresses, with salivary cortisol levels increasing by 2-fold at late gestation compared to nonpregnancy. Because normal diurnal variation of cortisol levels are maintained during pregnancy, pregnancy-related increases in cortisol are most evident in the morning. Thus, among pregnant women, sampling in the morning may create a “ceiling effect”, resulting in the inability to detect cortisol responses to stress. Thus, future studies of physiological reactivity in pregnancy should consider evaluation of women in the afternoon.

5. Stress Reactivity and Birth Outcomes

Maternal psychosocial stress has been associated with increased risk of preterm birth and low birth weight in more than three dozen studies [for review see 11, 12]. Demonstrating the magnitude of these effects, a meta-analysis of 29 studies concluded that depression during pregnancy poses a risk for preterm birth and low birth weight comparable to smoking 10 cigarettes per day [12]. These relationships remain after accounting for health behaviors, suggesting a role for direct physiological links between stress and adverse pregnancy outcomes.

Supporting an individual differences approach to understanding stress reactivity during pregnancy, emerging evidence has linked exaggerated physiological reactivity to increased risk of preterm delivery and low birth weight (Table 1). In the largest study of this kind to-date, 313 pregnant active-duty military women were assessed at 28 weeks gestation [26]. Each completed two common laboratory stressors, mental arithmetic task and a Stroop color word-matching task, while blood pressure and heart rate were monitored. Consistent with findings in non-pregnant samples, black women ($n = 75$) exhibited greater systolic and diastolic blood pressure reactivity than whites ($n = 238$). Moreover, among blacks only, greater blood pressure reactivity was associated with shorter gestation; each 1mmHg increase in diastolic blood pressure predicted a reduction in gestational age of .017 weeks.

McCubbin and colleagues examined cardiovascular reactivity to an arithmetic task among 40 healthy pregnant women who were assessed once at any timepoint in pregnancy [68].

Results demonstrated that each 1mmHg increase in diastolic blood pressure above the group mean in response to the stressor predicted a decrease of 80g in birth weight and a decrease of 0.314 weeks gestation. In addition, an interaction between diastolic reactivity and race was evidenced, suggesting a stronger association among African American women.

In an Argentinian study, blood pressure responses to a cold pressor test (CPT), involving immersion of the woman's hand in cold water for 3 minutes, were examined in 70 healthy women assessed between 23–40 weeks gestation. Every unit increase in diastolic blood pressure reactivity to the CPT was associated with a 47 gram decrease in birth weight and a 0.07 week decrease in gestational age at delivery as well as 0.09 cm decrease in the cephalic perimeter at birth [93].

Harville and colleagues examined stress reactivity in 917 non-pregnant women who subsequently had at least one singleton birth using data from the Coronary Artery Risk Development in Young Adult (CARDIA) study. Their results showed higher pre-pregnancy diastolic blood pressure and greater mean arterial pressure reactivity predicted greater likelihood of preterm birth at first pregnancy [94]. However, stress reactivity did not differentially predict risk of preterm birth in Blacks versus Whites.

Stress reactivity may also have predictive value for labor onset among full-term women. In a study of 74 women assessed at 38 weeks gestation, skin conductance activity during a cold pressor test, skin conductance activity decreased significantly with the number of days left to spontaneous onset of labor.[95].

Thus, these emerging data suggest that greater physiological stress responses are predictive of poorer birth outcomes. This may be predictive as a stable trait which exists prior to pregnancy and/or present risk among women who fail to show down-regulation of the stress response during a particular pregnancy. Notably, studies examining stress reactivity in association with birth outcomes have focused on heart rate and blood pressure responses rather than neuroendocrine or immune parameters. From a methodological standpoint, cardiovascular variables can be measured in inexpensive and non-invasive manner. However, the extent to which cardiovascular reactivity directly influences fetal development and birth outcomes is unknown. Although maternal cardiovascular function can affect fetal development directly [96], acute stressors also activate the HPA and SAM axes. Neuroendocrine mediators may ultimately play a greater causal role and/or provide greater prognostic value for adverse outcomes.

6. Stress Reactivity and Maternal Health

6.1. Gestational Hypertension

Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, are responsible for 10–15% of pregnancy-related deaths worldwide and are a leading cause of medically-indicated premature delivery [97]. Affecting 5–10% of all pregnancies in the United States, preeclampsia is a particularly serious condition marked by hypertension as well as edema and high levels of protein in the urine (proteinuria) which indicates kidney dysfunction. Animal studies support the hypothesis that excessive stimulation of the nervous system may contribute to hypertensive disorders in pregnancy. For example, pregnant rats exposed to the stress of cold stimulation of the paws for two weeks developed symptoms similar to preeclampsia [98, 99].

Some studies in women support this association. In a sample of 623 Finnish women, those who reported higher levels of anxiety or depressive symptoms early in pregnancy, prior to the development of preeclampsia, were 2–3 times more likely to develop the disorder than

their less anxious or depressed counterparts [10]. In a retrospective study of 717 women, those reporting greater work stress in the first trimester experienced increased risk of preeclampsia in the third trimester [9]. In particular, having a job characterized by both low decisional-latitude and high job pressure was associated with greater risk [9]. While not found in all studies [100], evidence also supports a link between self-reported stressful life events and likelihood of preeclampsia [8]. Similar results were found using objectively determined stress; among 5,804 pregnant Israeli women living in a war environment, those classified as living in higher risk areas had higher blood pressure than women living in lower risk areas [101]. Null findings are also reported; among 3,679 nulliparous women in the Netherlands, neither work stress, anxiety, depression, nor pregnancy-related anxiety were associated with preeclampsia or gestational hypertension [102].

To assess stress reactivity as a predictor of risk of preeclampsia, Woisetschlager and colleagues assessed 123 pregnant women between 16–20 weeks gestation [60]. Each completed a cold pressor test, involving application of an ice bag to the forehead for 3 minutes, while blood pressure and heart rate were monitored. Results demonstrated that both diastolic and systolic blood pressure responses were markedly greater among women who went on to develop preeclampsia (systolic blood pressure: 14.2 ± 5.5 versus 8.5 ± 7.2 mmHg, $p = 0.02$; diastolic blood pressure: 7.3 ± 4.9 versus 3.9 ± 4.7 mmHg, $p = 0.03$). Thus, in this study, a differential stress response pattern was present prior to the clinical manifestations of disease, indicating that individual differences in response tendencies may predict and/or causally contribute to risk of adverse cardiovascular outcomes in pregnancy.

6.2. Postpartum Depression

Greater stress reactivity has been linked to risk of depression and anxiety disorders. For example, greater cortisol reactivity to acute stress was seen among girls at high risk for depression based on family history of the disorder [103]. Limited evidence suggests that women with a tendency toward exaggerated physiological responses to daily life stressors may be more vulnerable to postpartum depression. Women with greater cortisol responses to a standardized psychosocial stressor at mid-pregnancy had significantly greater symptoms of depression at two weeks after delivery [104]. Of note, numerous studies have demonstrated that lactation is associated with attenuated hypothalamic-pituitary-adrenal axis responses to both physical and psychological stressors in animals [e.g., 105]. Fewer studies have been conducted in humans. Available data indicate that stress responses are markedly attenuated among women immediately after a breastfeeding session, but not generally suppressed across the course of lactation [106]. Thus, a promising direction for future research is the study of postpartum mood and stress responsivity in the context of breastfeeding.

7. Stress Reactivity and Fetal Development

The study of stress reactivity in human pregnancy has clear implications for fetal development. Early “programming” processes that occur in response to the environment may set the course for physiological responses through adolescence and adulthood, affecting vulnerability to mental and physical health conditions throughout life [13–16]. Thus, it is plausible that exaggerated stress reactivity may alter development in the fetus via increased exposure to cortisol and other stress mediators.

Numerous studies have demonstrated associations between maternal stress, anxiety, or depression and cognitive, emotional, and behavioral outcomes in offspring from fetal development through adolescence [for review see 107]. The role of maternal stress reactivity in these relationships is largely unknown. However, the developing fetus is physiologically responsive to even mild maternal stress. For example, among 137 pregnant women exposed to a mild psychological challenge (Stroop word-color task), fetuses showed increased heart

rate variability and suppression of motor activity [108]. Similar effects have been reported in other studies [109]. Although tendencies toward stress responding may, in part, be genetically inherited, repeated exposures to elevated cortisol and other stress mediators in utero may also influence fetal development.

Of interest from an intervention standpoint, the fetus is also responsive to maternal relaxation. In a study of 100 maternal-fetal pairs in which the women were exposed to an guided imagery relaxation procedure, both mothers and fetuses showed decreased heart rate and heart rate variability, with significant correlations between maternal and fetal responses [110]. In addition, an important consideration is that numerous studies indicate that the effect of maternal stress and/or exposure to maternal stress hormones during gestation differs among male and female offspring [111–113]. This may be a function of sex-specific differences in placental response (i.e., adaptive strategy) to an adverse maternal environment [114]. In addition, there is some evidence that females show more rapid neurodevelopment as compared to males and therefore may have heightened vulnerability [115]. Thus, studies are needed to delineate 1) the association of maternal stress reactivity with subsequent physiological functioning in offspring, 2) the effect of stress management interventions on the same parameters and 3) examination of the potential modifying role of sex in these relationships.

8. Additional Gaps in Knowledge

8.1 Gestational Stage

Data regarding stress reactivity in pregnancy is based primarily on studies from the third trimester. However, studies suggest that both the psychological experience of stress and the impact of physiological activation differ based on stage of gestation. For example, upon exposure to an earthquake, women rated the experience as more stressful in earlier versus later stages of pregnancy and showed increasingly shorter gestation upon earlier exposure [21]. This finding is consistent with the hypothesis that stress responsivity is progressively attenuated as pregnancy progresses. This suggests that exposure to stressors in early pregnancy may have greater implications for birth outcomes. Moreover, this highlights the need to understand individual differences in physiological adaptation across pregnancy, rather than at a single timepoint in gestation.

In relation to fetal development, implications of maternal stress activation differ considerably based on stage of gestation. In particular, 11β hydroxysteroid dehydrogenase type 2 (11β -HSD2) is active in the placenta, metabolizing cortisol before it reaches fetal circulation [116]. Thus, maternal levels of cortisol have been reported to be up to 28-fold higher than fetal levels [116–118]. The activity of 11β -HSD2 is greater in the second versus third trimester. The activity of this enzyme also shows great variability among individuals [119] and therefore may modify the association of maternal stress reactivity with developmental outcomes in the fetus. Moreover, by the third trimester, the influence of placentally-derived CRH on the production of cortisol is of sufficient magnitude to largely overpower effects of stress on cortisol levels [120]. Further emphasizing the critical role of timing of exposure, in a study of 125 full-term infants, exposure to elevated maternal cortisol in early gestation was associated with slower cognitive development in offspring over the first year of life, while elevated maternal cortisol in late gestation predicted accelerated development [121]. Thus, in future studies, effect of stage of gestation should be carefully considered in relation to the specific outcomes of interest.

8.2. Mechanistic Pathways

Physiological stress reactivity is multifaceted. The relative predictive value of cardiovascular versus neuroendocrine responses for adverse birth outcomes or fetal

development is unknown. In addition, the extent to which stress reactivity may serve as a marker of risk versus a causal mediator is not established. It is possible that maternal reactivity and birth outcomes are not causally linked, but instead share a common underlying mechanism such as genetic factors [68]. Alternatively, cardiovascular reactivity and/or neuroendocrine reactivity may directly affect perinatal health via transplacental mechanisms. Additional studies are needed to determine the role of maternal stress reactivity in the etiology of adverse birth outcomes and impaired fetal development.

8.3. Effects of Race

Substantial racial disparities in preterm birth and low birth weight are present in the U.S., with a preterm birth rate of approximately 18% among African-American women and 11–12% among non-Hispanic Whites [122]. Rates of low birthweight are similarly skewed, affecting 14% of African-American births versus 7.3% of non-Hispanic White births. These effects are not adequately explained by demographic factors (e.g., socioeconomic status) or traditional behavioral risk factors (e.g., early prenatal care, alcohol use, smoking, nutrition, or sexual practices) [for review see 122]. Theories have increasingly focused on the health implications of chronic stress associated with discriminated minority status [122–128]. Supporting the conceptualization of racial minority status as a chronic stressor, perceived racial discrimination has repeatedly been linked to increased risk of preterm delivery and low birth weight in African-American women [18, 127, 129–133]. Therefore, the role of race as predictor of individual differences in stress reactivity in pregnancy is highly justified.

Numerous studies of non-pregnant adults demonstrate that race and exposure to racism predict greater cardiovascular reactivity to acute stressors [134, 135]. In addition, stressors of a racially provocative nature elicit stronger cardiovascular responses among African Americans than do stressors that are racially neutral [135]. As described, emerging evidence suggests that the association between stress reactivity and gestational length may be more evident among African-American women than European-American women [26, 68]. This may represent inadequate attenuation of stress responsivity during pregnancy among African-Americans, or a tendency toward greater reactivity among African-American women in general. Future directions include the assessment of perceived racism as a predictor of reactivity among African-American women and comparison of responses to racially provoking stressors versus racially neutral stressors during pregnancy versus nonpregnancy. Moreover, via epigenetic programming of the neuroendocrine system during fetal development, maternal exposure to the chronic stress of racial discrimination during pregnancy may affect offspring health through adulthood, compounding the effects of racial discrimination across generations [136].

8.4. Buffers and Enhancers of the Stress Response

As reviewed, beyond race-related stress, varied measures of subjective stress are associated with risk of preterm delivery including perceived stress, pregnancy-specific anxiety, and depressive symptoms. Limited information is available regarding effects of such psychosocial factors on physiological reactivity in pregnancy. As reviewed, women high versus low in state anxiety showed differential blood pressure and fetal heart rate responses to an acute stressor [63]. These data are consistent with findings in non-pregnant populations which show that individual differences in psychosocial factors including hostility, depressive symptoms, and anxiety predict differential physiological responses to acute stress [75, 137–139].

In addition, psychosocial factors, particularly social support, may buffer the effects of stress [77]. Indeed, a large literature demonstrates that greater social support, measured quantitatively and qualitatively, predicts greater psychological well-being, better

cardiovascular health outcomes, and stronger immune function in the general population [140–142]. A possible mediator of this effect is via adaptive alterations in the physiological response to acute stressors [77, 143]. Although social support in pregnancy, particularly partner support, is a strong predictor of maternal mental health as well as birth outcomes [144–146], data regarding factors which may benefit the adaptation of the stress response across pregnancy are limited. One study demonstrated that women with greater social resources as indicated by greater self-efficacy and daily uplifts exhibited lesser cortisol responses to a public speaking task [71]. As key individual differences, future research should include more comprehensive assessment of psychosocial factors which may serve to buffer or exacerbate stress reactivity during pregnancy.

8.5 Assessment of Immune Parameters

Although preeclampsia is a leading cause of medically-indicated preterm delivery, microbiological studies indicate that 25–40% of preterm births may be related to intrauterine infection [124, 147]. Exaggerated stress reactivity may confer increased risk for preterm birth by 1) increasing susceptibility to infectious agents and 2) priming the inflammatory response to infectious agents [148]. With regard to susceptibility, psychosocial stress exposure has been associated with bacterial vaginosis in pregnant women [149, 150]. In non-pregnant adults, exaggerated stress reactivity predicts poorer cellular immune competence, as indicated by greater reactivation of latent Epstein-Barr Virus (EBV) [7].

In terms of inflammatory responding, substantial immune adaptation occurs during healthy pregnancy. Although pregnancy is characterized by increases in circulating levels of both pro and antiinflammatory cytokines [e.g., 151], inflammatory responses to *in vivo* and *in vitro* biological challenges in both humans and rodents appear to be attenuated during pregnancy as compared to nonpregnancy [44, 152–155]. In studies of non-pregnant adults, chronic stress and depressive symptoms predict exaggerated inflammatory responses to acute stress [156, 157]. In pregnancy, we have reported that depressive symptoms are associated with elevated serum proinflammatory cytokines as well as exaggerated inflammatory responses following influenza virus vaccination [158–160]. As with cardiovascular and neuroendocrine responses to stress, a great deal of variability is evidenced with regard to inflammatory responses to immune stimuli in pregnancy [158]. Identification of typical versus atypical responses may prove key to understanding risk for adverse outcomes. Examination of immune processes in relation to stress reactivity in pregnancy is currently lacking, but this focus is warranted.

8.6. Recovery following Stressors

Studies of reactivity in pregnancy have focused almost exclusively on magnitude of physiological change [for review see 51]. However, the ability to recover following acute stress also has important implications for health [4, 5]. Thus, assessment of not only the magnitude of response, but also the duration would greatly expand our understanding of the stress responses system in pregnancy.

8.7. Effects of Interventions

An ultimate goal of this line of research should be to provide interventions to counteract effects of maternal stress. Guided imagery has been shown to significantly improve subjective appraisals of relaxation and reduce maternal heart rate [110, 161]. A randomized controlled trial of relaxation and biofeedback for women with gestational hypertension showed lower blood pressure and less severe proteinuria in the intervention group [162]. Other modalities including acupuncture, exercise, massage, yoga, and psychotherapy have also been examined in relation to maternal mood, blood pressure, and birth outcomes [163]. However, the extent to which such interventions may benefit maternal and neonatal health

via alteration of the maternal stress response is unknown. Moreover, blunted physiological responses observed in the context of stressors may extend to relaxation, impacting the effectiveness of interventions. Among 54 women in late pregnancy compared to 28 non-pregnant controls, pregnant women showed lesser physiological changes (heart rate, respiratory sinus arrhythmia, and skin conductance) in response to an 18-minute guided imagery protocol despite similar subjective responses [164]. Thus intervention studies should consider the effects of pregnancy in their design.

8.8. Implications of Hypo- Reactivity

To-date, the literature on stress reactivity has focused almost exclusively on the adverse effects of excessive reactivity to stressors, whether measured in terms of cardiovascular or neuroendocrine responses. However, there is now an increasing recognition of the detrimental effects of blunted or inadequate responses to stressors [165]. Statistical models which examine stress reactivity in a linear fashion may underestimate or obscure findings when models would be better fit by a U-shaped association, with poorer outcomes at both ends of the response spectrum. Attention to hypo-reactivity as well as exaggerated reactivity as individual differences with consequences for health warrants attention in future studies.

8.9 Pregnancy as a “Stress Test”

As described, pregnancy is characterized by dramatic changes in neuroendocrine, cardiovascular, and immune function. As such, pregnancy itself may be conceptualized as a physiological “stress test” whereby a woman’s physiological response under these substantial demands predicts long-term risk of disease. A primary example in this regard is preeclampsia. Women who develop this serious hypertensive disorder during pregnancy have increased risk for hypertension, cardiovascular disease, cerebrovascular disease, renal and thromboembolic diseases, diabetes and all-cause mortality in later life [166–170]. Similarly, women who develop gestational diabetes mellitus (GDM) have increased risk of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases [171]. Of note, women exhibiting lesser degrees of glucose intolerance during pregnancy also show increased risks. It stands to be tested whether individual differences in response to pregnancy within the non-pathological range are predictive of long-term health.

9. Conclusions

The “reactivity hypothesis” has been applied to the study of health outcomes in the general population for decades. In pregnancy, stress reactivity may have unique implications for maternal health as well as for birth outcomes and fetal development. As reviewed in the current paper, our understanding of both the predictors and consequences of exaggerated stress reactivity in pregnancy is limited. Research in pregnancy to-date has focused primarily on stressor exposure. However, the impact of stress on health is ultimately a function of both exposure and response. Thus, increased attention to individual differences in stress reactivity will greatly advance our ability to both quantify the impact of stress for a given woman and predict women at greatest risk for adverse outcomes in the context of stress.

Available data indicate that cardiovascular and neuroendocrine responses to acute stressors are attenuated during healthy human pregnancy. Though limited, there are also data to support the hypothesis that greater cardiovascular reactivity during pregnancy is associated with shorter gestation, lower birth weight, increased risk of preeclampsia, and vulnerability for postpartum depression. In addition, upon maternal exposure to mild stressors, the physiological response of the fetus corresponds to that of the mother. Thus, via prenatal programming, maternal stress responses may have life-long effects on offspring health.

Ultimately, combining data regarding stress reactivity with information about frequency and severity of stressor exposure will provide the most robust understanding of effects of stress on maternal and offspring health.

Continued research in this area should incorporate more comprehensive assessment stress reactivity by including measures of both sympathetic nervous system activity and the HPA axis. Studies in this area would benefit from larger samples with carefully matched non-pregnant control groups. In addition, a focus on recovery following stressors would provide valuable information regarding individual differences in the duration of activation resulting from acute stress. Moreover, studies of stress reactivity in human pregnancy are generally lacking data on immune responses, heart rate variability, and measures of cardiac output and vascular resistance via impedance cardiography. Although it appears that physiological reactivity is attenuated during pregnancy on average, there is substantial variation across samples of pregnant women. However, there is limited information regarding effects of psychosocial factors (e.g., race, perceived stress, depressive symptoms, and anxiety) on adaptation of the stress response during pregnancy. Better describing typical adaptation of the maternal stress response and identifying predictors of atypical adaptation holds great promise for elucidating mechanistic pathways by which stress may affect maternal health, birth outcomes, and fetal development.

Acknowledgments

Manuscript preparation was supported by NICHD (R21HD061644 and R21HD067670). The content is solely the responsibility of the author and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

References

1. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*. 2008; 583(2–3):174–185. [PubMed: 18282566]
2. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull*. 2004; 130(4):601–630. [PubMed: 15250815]
3. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine*. 2003; 65:46–62. [PubMed: 12554815]
4. Linden W, Earle TL, Gerin W, Christenfeld N. Physiological stress reactivity and recovery: conceptual siblings separated at birth? *Journal of Psychosomatic Research*. 1997; 42(2):117–135. [PubMed: 9076640]
5. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*. 2004; 1032:1–7. [PubMed: 15677391]
6. Stewart JC, France CR. Cardiovascular recovery from stress predicts longitudinal changes in blood pressure. *Biological Psychology*. 2001; 58(2):105–120. [PubMed: 11600240]
7. Cacioppo JT, et al. Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. *Ann N Y Acad Sci*. 1998; 840:664–673. [PubMed: 9629293]
8. Hetzel BS, Bruer B, Poidevin L. A survey of the relation between certain common antenatal complications in primiparae and stressful life situations during pregnancy. *Journal of Psychosomatic Research*. 1961; 5:175–182. [PubMed: 13713965]
9. Landbergis PA. Psychosocial work stress and pregnancy-induced hypertension. *Epidemiology*. 1996; 7:346–351. [PubMed: 8793358]
10. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. *Obstetrics and Gynecology*. 2000; 95:487–490. [PubMed: 10725477]

11. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, van Geijin HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. *Journal of Psychosomatic Research*. 1995; 39:563–595. [PubMed: 7490693]
12. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. *Archives of General Psychiatry*. 2010; 67(10):1012–1024. [PubMed: 20921117]
13. Weinstock M. The potential influence of maternal stress hormones on development and mental health of offspring. *Brain, Behavior, and Immunity*. 2005; 19:296–308.
14. Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *Neuroendocrinology*. 2001; 13(2):113–128.
15. Bale TL, et al. Early Life Programming and Neurodevelopmental Disorders. *Biological Psychiatry*. 2010; 68(4):314–319. [PubMed: 20674602]
16. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci*. 2009; 3:14. [PubMed: 19738918]
17. Nordentoft M, Lou HC, Hansen D, Nim J, Pryds O, Rubin P, Hemmingsen R. Intrauterine growth retardation and premature delivery: the influence of maternal smoking and psychosocial factors. *American Journal of Public Health*. 1996; 86:347–354. [PubMed: 8604759]
18. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal stress and preterm birth. *American Journal of Epidemiology*. 2003; 157:14–24. [PubMed: 12505886]
19. Whitehead N, Hill HA, Brogan DJ, Blackmore-Prince C. Exploration of threshold analysis in the relation between stressful life events and preterm delivery. *American Journal of Epidemiology*. 2002; 155(2):117–124. [PubMed: 11790674]
20. Stein JA, Lu MC, Gelberg L. Severity of homelessness and adverse birth outcomes. *Health Psychology*. 2000; 19(6):524–534. [PubMed: 11129355]
21. Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Sandman CA. When stress happens matters: Effects of earthquake timing on stress responsivity during pregnancy. *American Journal of Obstetrics and Gynecology*. 2001; 184:637–642. [PubMed: 11262465]
22. Lederman SA, Rauh V, Weiss L, Stein JL, Hoepner LA, Becker M, Perera FP. The Effects of the World Trade Center Event on Birth Outcomes among Term Deliveries at Three Lower Manhattan Hospitals. *Environmental Health Perspectives*. 2004; 112:1772–1778. [PubMed: 15579426]
23. Anderson NB, Lane JD, Monou H, Williams RB, Houseworth SJ. Racial-Differences in Cardiovascular Reactivity to Mental Arithmetic. *International Journal of Psychophysiology*. 1988; 6(2):161–164. [PubMed: 3397318]
24. Lepore SJ, et al. Effects of social stressors on cardiovascular reactivity in Black and White women. *Annals of Behavioral Medicine*. 2006; 31(2):120–127. [PubMed: 16542126]
25. Light KC, Sherwood A. Race, borderline hypertension, and hemodynamic responses to behavioral stress before and after beta-adrenergic blockade. *Health Psychol*. 1989; 8(5):577–595. [PubMed: 2560975]
26. Hatch M, Berkowitz G, Janevic T, Sloan R, Lapinski R, James T, Barth WH. Race, cardiovascular reactivity, and preterm delivery among active-duty military women. *Epidemiology*. 2006; 17(2): 178–182. [PubMed: 16477258]
27. Light KC, Obrist PA, Sherwood A, James SA, Strogatz DS. Effects of race and marginally elevated blood pressure on responses to stress. *Hypertension*. 1987; 10(6):555–563. [PubMed: 3692569]
28. Lindsay JR, Nieman LK. The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. *Endocrine Reviews*. 2005; 26(6):775–799. [PubMed: 15827110]
29. McLean M, Bisits A, Davies J, RL Woods P, Smith R. A placental clock controlling the length of human pregnancy. *Nature Medicine*. 1995; 1(5):460–463.
30. McLean M, Smith R. Corticotrophin-releasing hormone and human parturition. *Reproduction*. 2001; 121(4):493–501. [PubMed: 11277868]
31. Magiakou MA, Mastorakos G, Webster E, Chrousos GP. The hypothalamic-pituitary-adrenal axis and the female reproductive system. *Annals of the New York Academy of Sciences*. 1997; 816:42–56. [PubMed: 9238254]

32. Mastorakos G, Ilias I. Maternal hypothalamic-pituitary-adrenal axis in pregnancy and the postpartum period - Postpartum-related disorders. *Young Woman at the Rise of the 21st Century: Gynecological and Reproductive Issues in Health and Disease*. 2000; 900:95–106.
33. Obel C, Hedegaard M, Henriksen TB, Secher NJ, Olsen J, Levine S. Stress and salivary cortisol during pregnancy. *Psychoneuroendocrinology*. 2005; 30(7):647–656. [PubMed: 15854781]
34. Nepomnaschy PA, Welch KB, McConnell DS, Low BS, Strassmann BI, England BG. Cortisol levels and very early pregnancy loss in humans. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(10):3938–3942. [PubMed: 16495411]
35. Hobel CJ, Goldstein A, Barrett ES. Psychosocial stress and pregnancy outcome. *Clinical Obstetrics and Gynecology*. 2008; 51(2):333–348. [PubMed: 18463464]
36. Lockwood CJ. Stress-associated preterm delivery: the role of corticotropin-releasing hormone. *American Journal of Obstetrics and Gynecology*. 1999; 180(1 Pt 3):S264–S266. [PubMed: 9914630]
37. Moutquin JM, Rainville C, Giroux L, Raynauld P, Amyot G, Bilodeau R, Pelland N. A Prospective-Study of Blood-Pressure in Pregnancy - Prediction of Preeclampsia. *American Journal of Obstetrics and Gynecology*. 1985; 151(2):191–196. [PubMed: 3970084]
38. Sibai BM, et al. Risk-Factors for Preeclampsia in Healthy Nulliparous Women - a Prospective Multicenter Study. *American Journal of Obstetrics and Gynecology*. 1995; 172(2):642–648. [PubMed: 7856699]
39. Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. *Lancet*. 1997; 349(9044):7–10. [PubMed: 8988114]
40. Hilmert CJ, Schetter CD, Dominguez TP, Abdou C, Hobel CJ, Glynn L, Sandman C. Stress and blood pressure during pregnancy: racial differences and associations with birthweight. *Psychosomatic Medicine*. 2008; 70(1):57–64. [PubMed: 18158373]
41. Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma-Catecholamine Responses to Physiological Stimuli in Normal Human-Pregnancy. *American Journal of Obstetrics and Gynecology*. 1986; 154(1):80–84. [PubMed: 3511708]
42. Oshaughnessy RW, Lehman E, Adams K, Scotttibbs GD, Zuspan FP. Plasma and Platelet Catecholamines in Normal and Preeclamptic Pregnancy. *Clinical and Experimental Hypertension Part B-Hypertension in Pregnancy*. 1984; 3(2–3):224–224.
43. Lederman RP, Lederman E, Work BA, Mccann DS. Plasma Epinephrine, Norepinephrine, and Cortisol of Multigravidas in Pregnancy and Labor and in Umbilical-Cord Arteries after Delivery. *Journal of Psychosomatic Obstetrics and Gynecology*. 1989; 10(1):57–69.
44. Elenkov IJ, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: Implications for autoimmune disease activity during these times. *Journal of Clinical Endocrinology and Metabolism*. 2001; 86(10):4933–4938. [PubMed: 11600565]
45. Lin B, Zhu S, Shao B. [Changes of plasma levels of monoamines in normal pregnancy and pregnancy-induced hypertension women and their significance]. *Zhonghua Fu Chan Ke Za Zhi*. 1996; 31(11):670–672. [PubMed: 9387528]
46. Wang L, Zhang W, Zhao Y. The study of maternal and fetal plasma catecholamines levels during pregnancy and delivery. *Journal of Perinatal Medicine*. 1999; 27(3):195–198. [PubMed: 10503181]
47. Nisell H, Hjemdahl P, Linde B, Lunell NO. Sympatho-Adrenal and Cardiovascular Reactivity in Pregnancy-Induced Hypertension .1. Responses to Isometric-Exercise and a Cold Pressor Test. *British Journal of Obstetrics and Gynaecology*. 1985; 92(7):722–731. [PubMed: 4016033]
48. Kaaja RJ, Moore MP, Yandle TG, Ylikorkala O, Frampton CM, Nicholls MG. Blood pressure and vasoactive hormones in mild preeclampsia and normal pregnancy. *Hypertension in Pregnancy*. 1999; 18(2):173–187. [PubMed: 10476619]
49. Manyonda IT, Slater DM, Fenske C, Hole D, Choy MY, Wilson C. A role for noradrenaline in pre-eclampsia: towards a unifying hypothesis for the pathophysiology. *British Journal of Obstetrics and Gynaecology*. 1998; 105(6):641–648. [PubMed: 9647155]
50. Katz VL, Jenkins T, Haley L, Bowes WA. Catecholamine Levels in Pregnant Physicians and Nurses - a Pilot-Study of Stress and Pregnancy. *Obstetrics and Gynecology*. 1991; 77(3):338–342. [PubMed: 1992394]

51. de Weerth C, Buitelaar JK. Physiological stress reactivity in human pregnancy - a review. *Neuroscience and Biobehavioral Reviews*. 2005; 29:295–312. [PubMed: 15811500]
52. Rohde W, Ohkawa T, Dobashi K, Arai K, Okinaga S, Dorner G. Acute Effects of Maternal Stress on Fetal Blood Catecholamines and Hypothalamic Lh-Rh Content. *Experimental and Clinical Endocrinology*. 1983; 82(3):268–274. [PubMed: 6360698]
53. Neumann ID, Torner L, Wigger A. Brain oxytocin: Differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. *Neuroscience*. 2000; 95(2):567–575. [PubMed: 10658637]
54. Neumann ID, et al. Attenuated neuroendocrine responses to emotional and physical stressors in pregnant rats involve adenohipophysial changes. *Journal of Physiology (London)*. 1998; 508(1): 289–300. [PubMed: 9490853]
55. Eneroth-Grimfors E, Bevegard S, Nilsson BA. Evaluation of three simple physiologic tests as predictors of pregnancy-induced hypertension. A pilot study. *Acta Obstet Gynecol Scand*. 1988; 67(2):109–113. [PubMed: 3176922]
56. Greenwood JP, Stoker JB, Walker JJ, Mary DA. Sympathetic nerve discharge in normal pregnancy and pregnancy-induced hypertension. *J Hypertens*. 1998; 16(5):617–624. [PubMed: 9797173]
57. Kammerer M, Adams D, Castelberg Bv B, Glover V. Pregnant women become insensitive to cold stress. *BMC Pregnancy Childbirth*. 2002; 2(1):8. [PubMed: 12437774]
58. Nisell H, Hjemdahl P, Linde B. Cardiovascular Reactivity to Adrenaline and Noradrenaline in Pregnancy Induced Hypertension. *Clinical and Experimental Hypertension Part B-Hypertension in Pregnancy*. 1984; 3(2–3):221–221.
59. Saisto T, Kaaja R, Helske S, Ylikorkala O, Halmesmaki E. Norepinephrine, adrenocorticotropin, cortisol and beta-endorphin in women suffering from fear of labor: responses to the cold pressor test during and after pregnancy. *Acta Obstetricia Et Gynecologica Scandinavica*. 2004; 83(1):19–26. [PubMed: 14678082]
60. Woisetschlager C, et al. Increased blood pressure response to the cold pressor test in pregnant women developing pre-eclampsia. *Journal of Hypertension*. 2000; 18(4):399–403. [PubMed: 10779089]
61. Hartikainen-Sorri AL, Kirkinen P, Sorri M, Anttonen H, Tuimala R. No effect of experimental noise exposure on human pregnancy. *Obstetrics and Gynecology*. 1991; 77(4):611–615. [PubMed: 2002987]
62. DiPietro JA, Costigan KA, Gurewitsch ED. Fetal response to induced maternal stress. *Early Human Development*. 2003; 74(2):125–138. [PubMed: 14580752]
63. Monk C, Fifer WP, Myers MM, Sloan RP, Trien L, Hurtado A. Maternal stress responses and anxiety during pregnancy: effects on fetal heart rate. *Developmental Psychobiology*. 2000; 36(1): 67–77. [PubMed: 10607362]
64. Monk C, Fifer WP, Sloan RP, Myers MM, Bagiella E, Ellman L, Hurtado A. Physiologic responses to cognitive challenge during pregnancy: effects of task and repeat testing. *International Journal of Psychophysiology*. 2001; 40(2):149–159. [PubMed: 11165353]
65. Monk C, Fifer WP, Sloan RP, Myers MM, Ellman L. Stress-elicited fetal and maternal heart rate changes in anxious vs non-anxious women. *Psychosomatic Medicine*. 2001; 63(1):92–92.
66. Monk CW, Myers MM, Sloan RP, Ellman LM, Fifer WP. Effects of women's stress-elicited physiological activity and chronic anxiety on fetal heart rate. *Journal of Developmental and Behavioral Pediatrics*. 2003; 24:32–38. [PubMed: 12584483]
67. Nisell H, Hjemdahl P, Linde B, Beskow C, Lunell NO. Sympathoadrenal and Cardiovascular-Responses to Mental Stress in Pregnancy-Induced Hypertension. *Obstetrics and Gynecology*. 1986; 68(4):531–536. [PubMed: 3748504]
68. McCubbin JA, Lawson EJ, Cox S, Sherman JJ, Norton JA, Read JA. Prenatal maternal blood pressure response to stress predicts birth weight and gestational age: a preliminary study. *American Journal of Obstetrics and Gynecology*. 1996; 175(3 Pt 1):706–712. [PubMed: 8828438]
69. Matthews KA, Rodin J. Pregnancy alters blood pressure responses to psychological and physical challenge. *Psychophysiology*. 1992; 29(2):232–240. [PubMed: 1635966]

70. De Weerth C, Wied CCGD, Jansen LMC, Buitelaar JK. Cardiovascular and cortisol responses to a psychological stressor during pregnancy. *Acta Obstetrica Et Gynecologica Scandinavica*. 2007; 86(10):1181–1192. [PubMed: 17851798]
71. Nierop A, Wirtz PH, Bratsikas A, Zimmermann R, Ehlert U. Stress-buffering effects of psychosocial resources on physiological and psychological stress response in pregnant women. *Biological Psychology*. 2008; 78(3):261–268. [PubMed: 18462859]
72. Entringer S, et al. Attenuation of maternal psychophysiological stress responses and the maternal cortisol awakening response over the course of human pregnancy. *Stress*. 2010; 13(3):258–268. [PubMed: 20067400]
73. Kasprovicz AL, Manuck SB, Malkoff SB, Krantz DS. Individual differences in behaviorally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology*. 1990; 27(6):605–619. [PubMed: 2100346]
74. Saab PG, et al. Myocardial and Peripheral Vascular-Responses to Behavioral Challenges and Their Stability in Black-and-White Americans. *Psychophysiology*. 1992; 29(4):384–397. [PubMed: 1410171]
75. Davis MC, Matthews KA, McGrath CE. Hostile attitudes predict elevated vascular resistance during interpersonal stress in men and women. *Psychosomatic Medicine*. 2000; 62(1):17–25. [PubMed: 10705907]
76. Saab, PG.; Schneiderman, N. Biobehavioral stressors, laboratory investigation, and the risk of hypertension. In: Blascovich, J.; Katkin, ES., editors. *Cardiovascular reactivity to psychological stress & disease*. Washington, D.C.: American Psychological Association; 1993. p. 49-82.
77. Christian LM, Stoney CM. Social support versus social evaluation: Unique effects on vascular and myocardial response patterns. *Psychosomatic Medicine*. 2006; 68(6):914–921. [PubMed: 17079702]
78. Weber CS, et al. Low vagal tone is associated with impaired post stress recovery of cardiovascular, endocrine, and immune markers. *European Journal of Applied Physiology*. 2010; 109(2):201–211. [PubMed: 20052593]
79. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, Levy D. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation*. 1994; 90(2):878–883. [PubMed: 8044959]
80. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation*. 1996; 94(11):2850–2855. [PubMed: 8941112]
81. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology*. 1987; 59(4):256–262. [PubMed: 3812275]
82. Van Laar JO, Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. *Acta Obstet Gynecol Scand*. 2008; 87(3):300–306. [PubMed: 18307069]
83. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *American Journal of Cardiology*. 1995; 75(14):882–885. [PubMed: 7732994]
84. Maunder RG, Lancee WJ, Nolan RP, Hunter JJ, Tannenbaum DW. The relationship of attachment insecurity to subjective stress and autonomic function during standardized acute stress in healthy adults. *Journal of Psychosomatic Research*. 2006; 60(3):283–290. [PubMed: 16516661]
85. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *American Heart Journal*. 2000; 140(4 Suppl):77–83. [PubMed: 11011352]
86. Walther T, Wessel N, Baumert M, Stepan H, Voss A, Faber R. Longitudinal analysis of heart rate variability in chronic hypertensive pregnancy. *Hypertension Research*. 2005; 28(2):113–118. [PubMed: 16025737]
87. Stein PK, Hagley MT, Cole PL, Domitrovich PP, Kleiger RE, Rottman JN. Changes in 24-hour heart rate variability during normal pregnancy. *American Journal of Obstetrics and Gynecology*. 1999; 180(4):978–985. [PubMed: 10203667]

88. Ekholm EM, Hartiala J, Huikuri HV. Circadian rhythm of frequency-domain measures of heart rate variability in pregnancy. *British Journal of Obstetrics and Gynaecology*. 1997; 104(7):825–828. [PubMed: 9236648]
89. Klinkenberg AV, Nater UM, Nierop A, Bratsikas A, Zimmermann R, Ehlert U. Heart rate variability changes in pregnant and non-pregnant women during standardized psychosocial stress. *Acta Obstetrica et Gynecologica Scandinavica*. 2009; 88(1):77–82. [PubMed: 19023678]
90. Pal GK, Pal P, Nanda N, Amudharaj D, Karthik S. Spectral analysis of heart rate variability (HRV) may predict the future development of essential hypertension. *Medical Hypotheses*. 2009; 72(2): 183–185. [PubMed: 18851902]
91. Lightman SL, Young WS 3rd. Lactation inhibits stress-mediated secretion of corticosterone and oxytocin and hypothalamic accumulation of corticotropin-releasing factor and enkephalin messenger ribonucleic acids. *Endocrinology*. 1989; 124(5):2358–2364. [PubMed: 2785027]
92. Webster JJ, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annual Review of Immunology*. 2002; 20:125–163.
93. Gomez Ponce de Leon R, Gomez Ponce de Leon L, Coviello A, De Vito E. Vascular maternal reactivity and neonatal size in normal pregnancy. *Hypertension in Pregnancy*. 2001; 20(3):243–256. [PubMed: 12044333]
94. Harville EW, Gunderson EP, Matthews KA, Lewis CE, Carnethon M. Pre-pregnancy stress reactivity and pregnancy outcome. *Paediatric and Perinatal Epidemiology*. 2010; 24(6):564–571. [PubMed: 20955234]
95. Hellgren C, Akerud H, Jonsson M, Poromaa IS. Sympathetic reactivity in late pregnancy is related to labour onset in women. *Stress-the International Journal on the Biology of Stress*. 2011; 14(6): 627–633.
96. Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn-Cook C, Saunders LD. Impact of pregnancy-induced hypertension on fetal growth. *American Journal of Obstetrics and Gynecology*. 1999; 180(1 Pt 1):207–213. [PubMed: 9914605]
97. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. *Seminars in Perinatology*. 2009; 33(3):130–137. [PubMed: 19464502]
98. Kanayama N, Tsujimura R, She L, Maehara K, Terao T. Cold-induced stress stimulates the sympathetic nervous system, causing hypertension and proteinuria in rats. *Journal of Hypertension*. 1997; 15:383–389. [PubMed: 9211173]
99. Khatun S, Kanayama N, Belayet HM, Masui M, Sugimura M, Kobayashi T, Terao T. Induction of preeclampsia like phenomena by stimulation of sympathetic nerve with cold and fasting stress. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 1999; 86:89–97.
100. Nisell H, Larsson G, Wager J. The relation between life stress and hypertensive complications during pregnancy. *Acta Obstetrica et Gynaecologica Scandinavica*. 1989; 68:423–427.
101. Rofe Y, Goldberg J. Prolonged exposure to a war environment and its effects on the blood pressure of pregnant women. *British Journal of Medical Psychology*. 1983; 56:305–311. [PubMed: 6661400]
102. Vollebregt KC, van der Wal MF, Wolf H, Vrijkotte TGM, Boer K, Bonsel GJ. Is psychosocial stress in first ongoing pregnancies associated with pre-eclampsia and gestational hypertension? *BJOG-an International Journal of Obstetrics and Gynaecology*. 2008; 115(5):607–615. [PubMed: 18333942]
103. Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry*. 2008; 63(9): 847–851. [PubMed: 18005940]
104. Nierop A, Bratsikas A, Zimmermann R, Ehlert U. Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms? *Psychosomatic Medicine*. 2006; 68(6):931–937. [PubMed: 17132840]
105. Neumann ID, et al. Attenuated neuroendocrine responses to emotional and physical stressors in pregnant rats involve adeno-hypophyseal changes. *J Physiol*. 1998; 508(Pt 1):289–300. [PubMed: 9490853]
106. Heinrichs M, Neumann I, Ehlert U. Lactation and stress: protective effects of breast-feeding in humans. *Stress*. 2002; 5(3):195–203. [PubMed: 12186682]

107. Van de Bergh BRH, Mulder EJH, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. *Neuroscience and Biobehavioral Reviews*. 2005; 29:237–258. [PubMed: 15811496]
108. DiPietro JA, Costigan KA, Gurewitsch ED. Fetal response to induced maternal stress. *Early Human Development*. 2003; 74(2):125–138. [PubMed: 14580752]
109. Monk C, Myers MM, Sloan RP, Ellman LM, Fifer WP. Effects of women's stress-elicited physiological activity and chronic anxiety on fetal heart rate. *Journal of Developmental and Behavioral Pediatrics*. 2003; 24(1):32–38. [PubMed: 12584483]
110. DiPietro JA, Costigan KA, Nelson P, Gurewitsch ED, Laudenslager ML. Fetal responses to induced maternal relaxation during pregnancy. *Biological Psychology*. 2008; 77(1):11–19. [PubMed: 17919804]
111. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109(20):E1312–E1319. [PubMed: 22529357]
112. Trautman PD, Meyer-Bahlburg HF, Postelnek J, New MI. Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children: results of a pilot study. *Psychoneuroendocrinology*. 1995; 20(4):439–449. [PubMed: 8532827]
113. Bale TL. Sex differences in prenatal epigenetic programming of stress pathways. *Stress*. 2011; 14(4):348–356. [PubMed: 21663536]
114. Clifton VL. Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival. *Placenta*. 2010; 31 Suppl:S33–S39. [PubMed: 20004469]
115. Buss C, Davis EP, Class QA, Gierczak M, Pattillo C, Glynn LM, Sandman CA. Maturation of the human fetal startle response: evidence for sex-specific maturation of the human fetus. *Early Human Development*. 2009; 85(10):633–638. [PubMed: 19726143]
116. Gitau R, Cameron A, Fisk NM, Glover V. Fetal exposure to maternal cortisol. *Lancet*. 1998; 352(9129):707–708. [PubMed: 9728994]
117. Gitau R, Fisk NM, Teixeira JMA, Cameron A, Glover V. Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. *Journal of Clinical Endocrinology and Metabolism*. 2001; 86(1):104–109. [PubMed: 11231985]
118. Glover V, Bergman K, Sarkar P, O'Connor TG. Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology*. 2009; 34(3):430–435. [PubMed: 19019559]
119. Welberg LA, Seckl JR, Holmes MC. Inhibition of 11 β -hydroxysteroid dehydrogenase, the foeto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. *European Journal of Neuroscience*. 2000; 12(3):1047–1054. [PubMed: 10762336]
120. Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. *Psychosomatic Medicine*. 1996; 58(5):432–446. [PubMed: 8902895]
121. Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development*. 2010; 81(1):131–148. [PubMed: 20331658]
122. Behrman, RE.; Butler, AS., editors. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. *Preterm birth : causes, consequences, and prevention*. Washington, D.C.: National Academies Press; 2007.
123. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. *Annual Review of Psychology*. 2011; 62:531–558.
124. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008; 371:75–84. [PubMed: 18177778]
125. Simhan HN, Krohn MA, Roberts JM, Zeevi A, Caritis SN. Interleukin-6 promoter-174 polymorphism and spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*. 2003; 189(4):915–918. [PubMed: 14586325]

126. Mulherin Engel SA, Erichsen HC, Savitz DA, Thorp J, Chanock SJ, Olshan AF. Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms. *Epidemiology*. 2005; 16(4):469–477. [PubMed: 15951664]
127. Giscombe CL, Lobel M. Explaining Disproportionately High Rates of Adverse Birth Outcomes Among African Americans: The Impact of Stress, Racism, and Related Factors in Pregnancy. *Psychological Bulletin*. 2005; 131(5):662–683. [PubMed: 16187853]
128. Green NS, et al. Research agenda for preterm birth: Recommendations from the March of Dimes. *American Journal of Obstetrics and Gynecology*. 2005; 193(3):626–635. [PubMed: 16150253]
129. Collins JW, David RJ, Handler A, Wall S, Andes S. Very low birthweight in African American infants: the role of maternal exposure to interpersonal racial discrimination. *American Journal of Public Health*. 2004; 94(12):2132–2138. [PubMed: 15569965]
130. Dole N, Savitz DA, Siega-Riz AM, Hertz-Picciotto I, McMahon MJ, Buekens P. Psychosocial factors and preterm birth among African American and White women in central North Carolina. *American Journal of Public Health*. 2004; 94(8):1358–1365. [PubMed: 15284044]
131. Mustillo S, Krieger N, Gunderson EP, Sidney S, McCreath H, Kiefe CI. Self-reported experiences of racial discrimination and Black-White differences in preterm and low-birthweight deliveries: the CARDIA Study. *American Journal of Public Health*. 2004; 94(12):2125–2131. [PubMed: 15569964]
132. Rosenberg L, Palmer JR, Wise LA, Horton NJ, Corwin MJ. Perceptions of racial discrimination and the risk of preterm birth. *Epidemiology*. 2002; 13(6):646–652. [PubMed: 12410005]
133. Dominguez TP, Schetter CD, Mancuso R, Rini CM, Hobel C. Stress in African American pregnancies: testing the roles of various stress concepts in prediction of birth outcomes. *Annals of Behavioral Medicine*. 2005; 29(1):12–21. [PubMed: 15677296]
134. Anderson NB. Racial differences in stress-induced cardiovascular reactivity and hypertension: current status and substantive issues. *Psychological Bulletin*. 1989; 105(1):89–105. [PubMed: 2648440]
135. Brondolo E, Rieppi R, Kelly KP, Gerin W. Perceived racism and blood pressure: A review of the literature and conceptual and methodological critique. *Annals of Behavioral Medicine*. 2003; 25(1):55–65. [PubMed: 12581937]
136. Kramer MR, Hogue CJ, Dunlop AL, Menon R. Preconceptional stress and racial disparities in preterm birth: an overview. *Acta Obstet Gynecol Scand*. 2011; 90(12):1307–1316. [PubMed: 21446927]
137. Berntson GG, Sarter M, Cacioppo JT. Anxiety and cardiovascular reactivity: the basal forebrain cholinergic link. *Behavioural Brain Research*. 1998; 94(2):225–248. [PubMed: 9722275]
138. Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*. 2005; 30(9):846–856. [PubMed: 15961250]
139. Kibler JL, Ma M. Depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. *International Journal of Behavioral Medicine*. 2004; 11(2):81–87. [PubMed: 15456676]
140. Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: Toward a lifespan approach. *Journal of Behavioral Medicine*. 2006; 29
141. Krantz DS, Manuck SB. Acute psychophysiological reactivity and risk of cardiovascular disease: a review and methodologic critique. *Psychological Bulletin*. 1984; 96(3):435–464. [PubMed: 6393178]
142. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin*. 1996; 119(3):488–431. [PubMed: 8668748]
143. Kamarck TW, Manuck SB, Jennings JR. Social support reduces cardiovascular reactivity to psychological challenge: A laboratory model. *Psychosomatic Medicine*. 1990; 52(1):42–58. [PubMed: 2305022]
144. Collins NL, Dunkel-Schetter C, Lobel M, Scrimshaw S. Social support in pregnancy: Psychosocial correlates of birth outcomes and postpartum depression. *Journal of Personality and Social Psychology*. 1993; 65:1243–1258. [PubMed: 8295121]

145. Feldman PJ, Dunkel-Schetter C, Sandman CA, Wadhwa PD. Maternal social support predicts birth weight and fetal growth in human pregnancy. *Psychosomatic Medicine*. 2000; 62:715–725. [PubMed: 11020102]
146. Stapleton LR, Schetter CD, Westling E, Rini C, Glynn LM, Hobel CJ, Sandman CA. Perceived partner support in pregnancy predicts lower maternal and infant distress. *J Fam Psychol*. 2012; 26(3):453–463. [PubMed: 22662772]
147. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000; 342(20):1500–1507. [PubMed: 10816189]
148. Christian LM. Psychoneuroimmunology in pregnancy: Immune pathways linking stress with maternal health, adverse birth outcomes, and fetal development. *Neuroscience and Biobehavioral Reviews*. 2012; 36
149. Culhane JF, Rauh V, McCollum KF, Hogan VK, Agnew K, Wadhwa PD. Maternal stress is associated with bacterial vaginosis in human pregnancy. *Maternal and Child Health Journal*. 2001; 5(2):127–134. [PubMed: 11573838]
150. Culhane JF, Rauh V, McCollum KF, Elo IT, Hogan V. Exposure to chronic stress and ethnic differences in rates of bacterial vaginosis among pregnant women. *American Journal of Obstetrics and Gynecology*. 2002; 187(5):1272–1276. [PubMed: 12439519]
151. Curry AE, et al. Maternal plasma cytokines in early- and mid-gestation of normal human pregnancy and their association with maternal factors. *Journal of Reproductive Immunology*. 2008; 77(2):152–160. [PubMed: 17692390]
152. Marzi M, Vigano A, Trabattini D, Villa ML, Salvaggio A, Clerici E, Clerici M. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clinical and Experimental Immunology*. 1996; 106(1):127–133. [PubMed: 8870710]
153. Makhseed M, Raghupathy R, Azizieh F, Al-Azemi MMK, Hassan NA, Bandar A. Mitogen-induced cytokine responses of maternal peripheral blood lymphocytes indicate a differential Th-type bias in normal pregnancy and pregnancy failure. *American Journal of Reproductive Immunology*. 1999; 42(5):273–281. [PubMed: 10584981]
154. Aguilar-Valles A, Poole S, Mistry Y, Williams S, Luheshi GN. Attenuated fever in rats during late pregnancy is linked to suppressed interleukin-6 production after localized inflammation with turpentine. *Journal of Physiology-London*. 2007; 583(1):391–403.
155. Fofie AE, Fewell JE, Moore SL. Pregnancy influences the plasma cytokine response to intraperitoneal administration of bacterial endotoxin in rats. *Experimental Physiology*. 2004; 90(1):95–101. [PubMed: 15466457]
156. Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry*. 2006; 163(9):1630–U1. [PubMed: 16946190]
157. Brydon L, Edwards S, Mohamed-Ali V, Steptoe A. Socioeconomic status and stress-induced increases in interleukin-6. *Brain, Behavior, and Immunity*. 2004; 18(3):281–290.
158. Christian LM, Iams JD, Porter K, Glaser R. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. *Vaccine*. 2011; 29:8982–8987. [PubMed: 21945263]
159. Christian LM, Franco A, Glaser R, Iams J. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. *Brain, Behavior, and Immunity*. 2009; 23(6):750–754.
160. Christian LM, Franco A, Iams JD, Sheridan J, Glaser R. Depressive symptoms predict exaggerated inflammatory response to in vivo immune challenge during human pregnancy. *Brain, Behavior, and Immunity*. 2010; 24(1):49–53.
161. Urech C, Fink NS, Hoesli I, Wilhelm FH, Bitzer J, Alder J. Effects of relaxation on psychobiological wellbeing during pregnancy: a randomized controlled trial. *Psychoneuroendocrinology*. 2010; 35(9):1348–1355. [PubMed: 20417038]
162. Little BC, Hayworth J, Benson P, Hall F, Beard RW, Dewhurst J, Priest RG. Treatment of hypertension in pregnancy by relaxation and biofeedback. *Lancet*. 1984; 1(8382):865–867. [PubMed: 6143184]

163. Beddoe AE, Lee KA. Mind-body interventions during pregnancy. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*. 2008; 37(2):165–175.
164. Dipietro JA, Mendelson T, Williams EL, Costigan KA. Physiological blunting during pregnancy extends to induced relaxation. *Biological Psychology*. 2012; 89:14–20. [PubMed: 21802489]
165. Lovallo WR. Do low levels of stress reactivity signal poor states of health? *Biological Psychology*. 2011; 86(2):121–128. [PubMed: 20079397]
166. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension*. 2010; 56(1):166–171. [PubMed: 20516394]
167. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007; 335(7627):974. [PubMed: 17975258]
168. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *American Heart Journal*. 2008; 156(5):918–930. [PubMed: 19061708]
169. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *New England Journal of Medicine*. 2008; 359(8):800–809. [PubMed: 18716297]
170. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, McIntyre HD. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. *American Journal of Obstetrics and Gynecology*. 2007; 197(5):492, e1–e7. [PubMed: 17980185]
171. Verier-Mine O. Outcomes in women with a history of gestational diabetes. Screening and prevention of type 2 diabetes. *Diabetes and Metabolism*. 2010; 36(6 Pt 2):595–616. [PubMed: 21163424]

Abbreviations List

TSST	Trier Social Stress Test
CO	Cardiac output
TPR	Total peripheral resistance
HRV	Heart rate variability
HPA	Hypothalamic-pituitary-adrenal
GR	Glucocorticoid receptor
CPT	Cold pressor test
PTB	Preterm birth

Highlights

Physiological responses to stressors predict adverse health outcomes in nonpregnant adults.

Significant cardiovascular and neuroendocrine adaptation is seen in healthy pregnancy.

Stress responses in pregnant women may affect birth outcomes and maternal/fetal health.

Explication of predictors and consequences of exaggerated stress reactivity in pregnancy is needed.

The HPA Axis

Placental production of CRH stimulates ACTH from the maternal pituitary, in turn stimulating production of cortisol from the adrenal glands resulting in hypercortisolism and eventual hypertrophy of the pituitary and adrenal glands.

Cardiovascular System

Blood volume increases by ~45%. Cardiac output increases by 30-50% while systemic vascular resistance decreases. An overall decrease in blood pressure is seen with a nadir at mid-gestation.

Figure 1.
Basal Physiological Adaptation During Pregnancy.

Table 1**Studies of Stress Reactivity and Birth Outcomes**

Study	Subjects	Stressor	Measures	Results
Gomez Ponce de Leon [93]	70 healthy pregnant women	Cold pressor test	Blood pressure	<ul style="list-style-type: none"> • Mean blood pressure increases were negatively associated with gestation age and head circumference at birth. • Diastolic blood pressure increases were negatively correlated with newborn weight.
Harville et al. [94]	917 women assessed prior to pregnancy	Video game, star tracing, and cold pressor test	Blood pressure Heart rate	<ul style="list-style-type: none"> • Higher mean arterial pressure reactivity was associated with risk of PTB at first delivery. • Small for gestational age was associated with lower systolic blood pressure reactivity.
Hatch et al. [26]	313 active-duty military women (75 black; 238 white)	Mental arithmetic and Stroop color-word task	Blood pressure Heart rate	<ul style="list-style-type: none"> • In blacks only, greater diastolic blood pressure reactivity predicted shorter gestation.
McCubbin et al. [68]	40 healthy pregnant women	Arithmetic task	Blood pressure Heart rate	<ul style="list-style-type: none"> • Larger diastolic blood pressure responses were associated with lower birth weight and decreased gestational age at delivery.