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Physiological reactivity to psychological stress in human pregnancy: Current knowledge and future directions

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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.

Contents

Abbreviations: 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.

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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 (McEwen, 2004, 2008; Segerstrom and Miller, 2004; Treiber et al., 2003; Linden et al., 1997; Stewart and France, 2001; Cacioppo et al., 1998).

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 (Hetzel et al., 1961; Landbergis, 1996; Kurki et al., 2000; Paarlberg et al., 1995; Grote et al., 2010; Weinstock, 2005; Welberg and Seckl, 2001; Bale et al., 2010; Bilbo and Schwarz, 2009). Thus, differential reactivity to daily life stressors may have unique implications in the context of pregnancy. 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.

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 (Nordentoft et al., 1996; Dole et al., 2003; Whitehead et al., 2002). Similarly, exposure to chronic (e.g., homelessness) or catastrophic (e.g., earthquake, terrorist attack) events has been associated with adverse birth outcomes (Stein et al., 2000; Glynn et al., 2001; Lederman et al., 2004). 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 (Anderson et al., 1988; Lepore et al., 2006; Light and Sherwood, 1989; Hatch et al., 2006; Light et al., 1987). 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 (Fig. 1). Placental production of corticotropin-releasing hormone (CRH) increases exponentially as pregnancy progresses, with up to 1000-fold increases in plasma CRH by term (Lindsay and Nieman, 2005). 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 (McLean et al., 1995; McLean and Smith, 2001). Notably, placentally-derived CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity (Lindsay and Nieman, 2005; Magiakou et al., 1997). 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 adrenocorticotropic 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 2–3-fold higher than nonpregnancy by term (Mastorakos and Ilias, 2000). 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 (Obel et al., 2005) and higher cortisol early in gestation has been linked to risk of spontaneous abortion (Nepomnaschy et al., 2006). Moreover, it has been suggested that placental-production of CRH is a stress-sensitive, thus influencing the timing of parturition (Hobel et al., 2008; Lockwood, 1999).

The maternal cardiovascular system also undergoes substantial changes to support fetal development during pregnancy (Fig. 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 (Moutquin et al., 1985; Sibai et al., 1995). Moreover, higher blood pressure has been associated with lower birth weight, even among normotensive women (Churchill et al., 1997; Hilmert et al., 2008). 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 (Hilmert et al., 2008). 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 (Barron et al., 1986; Oshaughnessy et al., 1984; Lederman et al., 1989), and increasing

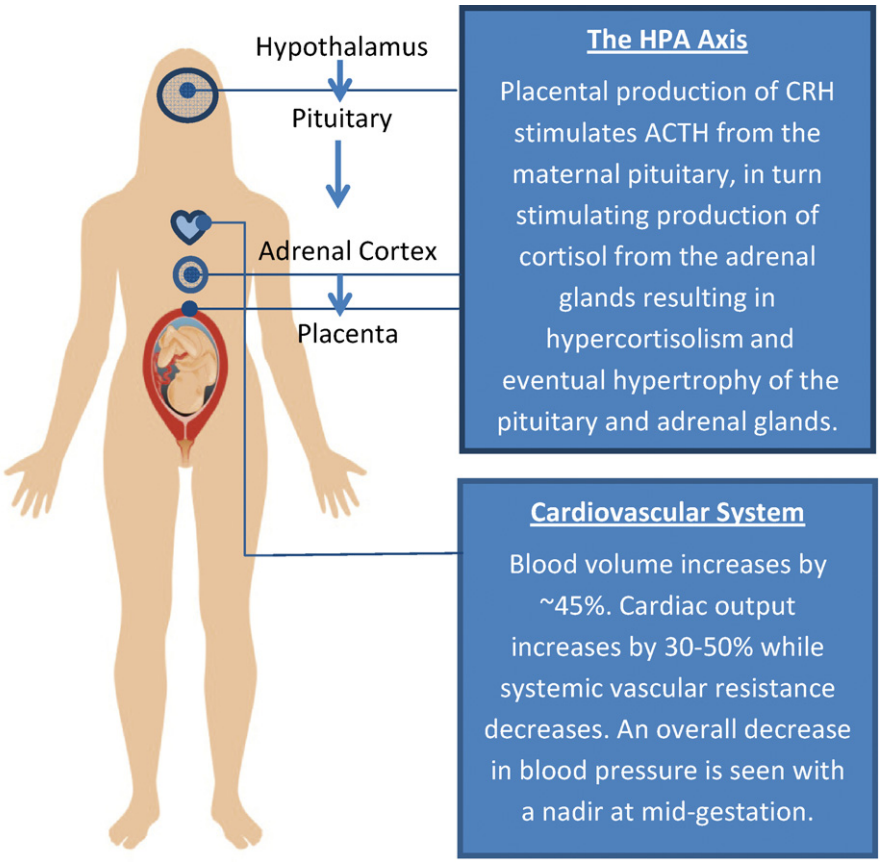

Fig. 1. Basal physiological adaptation during pregnancy.

(Elenkov et al., 2001; Lin et al., 1996) or decreasing (Wang et al., 1999; Nisell et al., 1985) 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 (Kaaja et al., 1999; Manyonda et al., 1998). Further, elevations in catecholamines during pregnancy have been associated with occupational stress (Katz et al., 1991).

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 (de Weerth and Buitelaar, 2005). Similarly, dampened responsivity has been reported in rodents (Rohde et al., 1983; Neumann et al., 1998a, 2000). 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 (Eneroth-Grimfors et al., 1988; Greenwood et al., 1998; Kammerer et al., 2002; Saisto et al., 2004; Woisetschlager et al., 2000; Hartikainen-Sorri et al., 1991; DiPietro et al., 2003; Monk et al., 2000, 2001, 2003a; Nisell et al., 1986; McCubbin et al., 1996; Matthews and Rodin, 1992; De Weerth et al., 2007; Nierop et al., 2008; Entringer et al., 2010). 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 (Matthews and Rodin, 1992). 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 (Entringer et al., 2010). 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 (de Weerth and Buitelaar, 2005), 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 (Kasprowicz et al., 1990). A tendency toward vascular responding has been reported among those at greater risk for cardiovascular diseases, including Blacks compared to Whites (Saab et al., 1992) and high hostile compared to low-hostile adults (Davis et al., 2000). Vascular responding may result in detrimental health effects in several ways, including slower habituation to stress and promotion of endothelial dysfunction (Saab and Schneiderman, 1993). Thus, frequent or extended peripheral vasoconstriction may lead to increases in resting peripheral resistance over time, resulting in hypertension (Saab and Schneiderman, 1993).

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 (Christian and Stoney, 2006). 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., Hilmert et al., 2008; McCubbin et al., 1996). 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 (Weber et al., 2010). In relation to health outcomes, low HRV is associated with many pathological conditions and predicts risk for all-cause mortality in the elderly (Tsuji et al., 1994), risk for cardiac events in the general population (Tsuji et al., 1996) and poor prognosis in patients with heart disease (Kleiger et al., 1987). In addition, diminished HRV has been recognized as an indicator of fetal distress for decades (Van Laar et al., 2008). 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 (Kawachi et al., 1995; Maunder et al., 2006; Gorman and Sloan, 2000).

Corresponding to increases in resting heart rate as pregnancy progresses, heart rate variability decreases with gestational age in healthy pregnancies (Walther et al., 2005; Stein et al., 1999; Ekholm et al., 1997). Differential changes in heart rate variability over the course of gestation have been reported among women with versus without gestational hypertension (Walther et al., 2005). 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 (Klinkenberg et al., 2009). 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 (Pal et al., 2009).

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 (Kammerer et al., 2002). Similarly, down-regulation of the HPA response system has repeatedly been observed in both pregnant and lactating rats (e.g., Neumann et al., 1998a, 2000; Lightman and Young, 1989). Similarly, attenuated catecholamine responses have been observed in pregnant women in response to psychological and physiological stressors (e.g., Barron et al., 1986; Nisell et al., 1986). 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 (Webster et al., 2002). 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 (Paarlberg et al., 1995; Grote et al., 2010). 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 $\geq$10 cigarettes per day (Grote et al., 2010). 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

Table 1
Studies of stress reactivity and birth outcomes.

Study	Subjects	Stressor	Measures	Results
Gomez Ponce de Leon et al. (2001)	70 healthy pregnant women	Cold pressor test	Blood pressure	• 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. (2010)	917 women assessed prior to pregnancy	Video game, star tracing, and cold pressor test	Blood pressure Heart rate	• 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. (2006)	313 active-duty military women (75 black; 238 white)	Mental arithmetic and Stroop color-word task	Blood pressure Heart rate	• In blacks only, greater diastolic blood pressure reactivity predicted shorter gestation.
McCubbin et al. (1996)	40 healthy pregnant women	Arithmetic task	Blood pressure Heart rate	• Larger diastolic blood pressure responses were associated with lower birth weight and decreased gestational age at delivery.

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 (Hatch et al., 2006). 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 1 mmHg increase in diastolic blood pressure predicted a reduction in gestational age of 0.017 weeks.

McCubbin et al. examined cardiovascular reactivity to an arithmetic task among 40 healthy pregnant women who were assessed once at any timepoint in pregnancy (McCubbin et al., 1996). Results demonstrated that each 1 mmHg increase in diastolic blood pressure above the group mean in response to the stressor predicted a decrease of 80 g 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 Argentinean study, blood pressure responses to a cold pressor test (CPT), involving immersion of the woman's hand in cold water for 3 min, were examined in 70 healthy women assessed between 23 and 40 weeks gestation. Every unit increase in diastolic blood pressure reactivity to the CPT was associated with a 47 g 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 (Gomez Ponce de Leon et al., 2001).

Harville et al. 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 (Harville et al., 2010). 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 (Hellgren et al., 2011).

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 (Xiong et al., 1999), 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 (Duley, 2009). 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 (Kanayama et al., 1997; Khatun et al., 1999).

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 (Kurki et al., 2000). 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 (Landbergis, 1996). In particular, having a job characterized by both low decisional-latitude and high job pressure was associated with greater risk (Landbergis, 1996). While not found in all studies (Nisell et al., 1989), evidence also supports a link between self-reported stressful life events and likelihood of preeclampsia (Hetzel et al., 1961). Similar results were found using objectively determined stress; among 5804 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 (Rofe and Goldberg, 1983). Null findings are also reported; among 3679 nulliparous women in the Netherlands, neither work stress, anxiety, depression, nor pregnancy-related anxiety were associated with preeclampsia or gestational hypertension (Vollebregt et al., 2008).

To assess stress reactivity as a predictor of risk of preeclampsia, Woisetschlager et al. assessed 123 pregnant women between 16 and 20 weeks gestation (Woisetschlager et al., 2000). Each completed a cold pressor test, involving application of an ice bag to the forehead for 3 min, 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 (Gotlib et al., 2008). 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 (Nierop et al., 2006). 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., Neumann et al., 1998b). 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 (Heinrichs et al., 2002). 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 (Weinstock, 2005; Welberg and Seckl, 2001; Bale et al., 2010; Bilbo and Schwarz, 2009). 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 (Van den Bergh et al., 2005). 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 (DiPietro et al., 2003). Similar effects have been reported in other studies (Monk et al., 2003b). 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 a guided imagery relaxation procedure, both mothers and fetuses showed decreased heart rate and heart rate variability, with significant correlations between maternal and fetal responses (DiPietro et al., 2008). 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 (Buss et al., 2012; Trautman et al., 1995; Bale, 2011). This may be a function of sex-specific differences in placental response (i.e., adaptive strategy) to an adverse maternal environment (Clifton, 2010). In addition, there is some evidence that females show more rapid neurodevelopment as compared to males and therefore may have heightened vulnerability (Buss et al., 2009). 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 (Glynn et al., 2001). 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 (Gitau et al., 1998). Thus, maternal levels of cortisol have been reported to be up to 28-fold higher than fetal levels (Gitau et al., 1998, 2001; Glover et al., 2009). The activity of 11β-HSD2 is greater in the second versus third trimester. The activity of this enzyme also shows great variability among individuals (Welberg et al., 2000) 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 (Wadhwa et al., 1996). 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 (Davis and Sandman, 2010). 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 link, but instead share a common underlying mechanism such as genetic factors (McCubbin et al., 1996). 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 (Committee, 2007). 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 (Committee, 2007). Theories have increasingly focused on the health implications of chronic stress associated with discriminated minority status (Committee, 2007; Dunkel Schetter, 2011; Goldenberg et al., 2008; Simhan et al., 2003; Mulherin Engel et al., 2005; Giscombe and Lobel, 2005; Green et al., 2005). 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 (Dole et al., 2003; Giscombe and Lobel, 2005; Collins et al., 2004; Dole et al., 2004; Mustillo et al., 2004; Rosenberg et al., 2002; Dominguez et al., 2005). 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 (Anderson, 1989; Brondolo et al., 2003). In addition, stressors of a racially provocative nature elicit stronger cardiovascular responses among African Americans than do stressors that are racially neutral (Brondolo et al., 2003). 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 (Hatch et al., 2006; McCubbin et al., 1996). 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 (Kramer et al., 2011).

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 (Monk et al., 2000). 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 (Davis et al., 2000; Berntson et al., 1998; Burke et al., 2005; Kibler and Ma, 2004).

In addition, psychosocial factors, particularly social support, may buffer the effects of stress (Christian and Stoney, 2006). 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 (Graham et al., 2006; Krantz and Manuck, 1984; Uchino et al., 1996). A possible mediator of this effect is via adaptive alterations in the physiological response to acute stressors (Christian and Stoney, 2006; Kamarck et al., 1990). Although social support in pregnancy, particularly partner support, is a strong predictor of maternal mental health as well as birth outcomes (Collins et al., 1993; Feldman et al., 2000; Stapleton et al., 2012), 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 (Nierop et al., 2008). 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 (Goldenberg et al., 2008, 2000). 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 (Christian, 2012). With regard to susceptibility, psychosocial stress exposure has been associated with bacterial vaginosis in pregnant women (Culhane et al., 2001, 2002). In non-pregnant adults, exaggerated stress reactivity predicts poorer cellular immune competence, as indicated by greater reactivation of latent Epstein–Barr Virus (EBV) (Cacioppo et al., 1998).

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., Curry et al., 2008), 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 (Elenkov et al., 2001; Marzi et al., 1996; Makhseed et al., 1999; Aguilar-Valles et al., 2007; Fofie et al., 2004). In studies of non-pregnant adults, chronic stress and depressive symptoms predict exaggerated inflammatory responses to acute stress (Pace et al., 2006; Brydon et al., 2004). 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 (Christian et al., 2009, 2010, 2011). 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 (Christian et al., 2011). 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

(de Weerth and Buitelaar, 2005). However, the ability to recover following acute stress also has important implications for health (Linden et al., 1997; McEwen, 2004). 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 (DiPietro et al., 2008; Urech et al., 2010). 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 (Little et al., 1984). Other modalities including acupuncture, exercise, massage, yoga, and psychotherapy have also been examined in relation to maternal mood, blood pressure, and birth outcomes (Beddoe and Lee, 2008). 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-min guided imagery protocol despite similar subjective responses (Dipietro et al., 2012). 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 (Lovallo, 2011). 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 (Mongraw-Chaffin et al., 2010; Bellamy et al., 2007; McDonald et al., 2008; Vikse et al., 2008; Callaway et al., 2007). Similarly, women who develop gestational diabetes mellitus (GDM) have increased risk of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases (Verier-Mine, 2010). 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 preeclampia, 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.

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