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Influence of Maternal Prior Life Adversity on the Psycho-Neuroendocrine-Immune Profile During Pregnancy

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INFLUENCE OF MATERNAL PRIOR LIFE ADVERSITY ON THE PSYCHO-NEUROENDOCRINE-IMMUNE PROFILE DURING PREGNANCY

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ABSTRACT

Pregnancy is accompanied by a multitude of physical and psychological changes. Adaptation to these changes through reduced anxiety and attenuated stress responsiveness is necessary across gestation and into the postpartum period for optimal maternal-infant health. In contrast, exposure to higher amounts of stressors during pregnancy can disrupt neuroendocrine-immune processes required for successful pregnancy outcomes. Evolving evidence demonstrates that exposure to adversity early in life has long-lasting effects on stress response systems that alter stress reactivity during adulthood. Given this evidence, it is posited that women who experience greater pre-pregnancy adversity during their childhood are at greater risk for negative maternal-infant health sequelae. Thus, the purpose of this study is to investigate the relationship between maternal childhood adversity and the psychological-neuroendocrine-immune profile during pregnancy. In addition, maternal risk and protective factors posited to moderate this profile were examined. Lastly, the relationship among maternal childhood adversity, maternal PNI profile during pregnancy, and neonatal outcomes were explored. The findings can contribute to improved approaches to identify and stratify risk for adverse maternal-infant health outcomes, as well as guide the development of early intervention programs and health policy for women who are pregnant or who plan to become pregnant. This is

significant because the well-being of mothers and infants determines the health of the next generation. Improving maternal-infant well-being can markedly reduce public health challenges and ultimately reduce health care costs across the lifespan (U.S. Department of Health and Human Services, 2011).

CHAPTER ONE

STATEMENT OF THE PROBLEM

A successful pregnancy is vital to the health of future generations and thus research to improve maternal infant health, including psychological well-being, is a national priority (U.S. Department of Health and Human Services, 2011). For most women, pregnancy is a profound life experience associated with upheavals of emotions, relationships and roles. Lederman (2009) identified seven dimensions of maternal emotional health: acceptance of the pregnancy, motivation to take on the role of motherhood, relationships with husband/partner, and own mother, preparation for labor, self-esteem, and sense of control. All of these have potential to impact delivery, postpartum adaptation, infant health, child development, and even adult health (Lederman, 2009). Thus, to ensure optimal maternal-newborn outcomes, pregnancy requires significant psychological and physiological adaptation.

Relevant to this proposal, maternal adaptations, such as decreased anxiety and attenuated stress responsiveness, are necessary to enable successful pre- and postnatal development of the offspring. A review of the chronic stress response, and how this influences neurodevelopment and behaviors, is available in Lupien et al. (2009).

Evidence demonstrates that maternal stressors negatively impacts pregnancy outcomes and subsequent child development (de Weerth & Buitelaar, 2005; Diego et al., 2006; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008).

It is possible that psycho-physiological adaptation to the experience of pregnancy may be impaired in women who experienced prior life adversity during their childhood. This supposition is supported by evidence derived from animal and human studies that identify early life adversity as a vulnerability factor that gives rise to an adult phenotype characterized by a heightened vulnerability to future stressful life experiences (Danese & McEwen, 2012; Heim, Shugart, Craighead, & Nemeroff, 2010). This stress-vulnerability has been attributed to alterations in neurobiological processes of the developing brain, which persist and shape responses to future life challenges (Danese & McEwen, 2012; Heim et al., 2010; Nemeroff, 2004). For example, adults who experienced childhood maltreatment or trauma were found to react with greater emotional responsiveness to stressful life events (McLaughlin et al., 2010). These individuals also manifested an altered physiological response to stressors, including increased autonomic nervous system activity and dysregulated hypothalamic-pituitary-adrenocortical (HPA) axis reactivity (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Further, individuals exposed to early life adversity are found to be at greater risk for depression and other mood disorders later in life, especially in the context of challenging life circumstances (Chen et al., 2010; Heim et al., 2010; Hill et al., 2000; Nemeroff, 2004). Recently, childhood adversity was shown to predispose to a proinflammatory phenotype. Lower childhood socioeconomic status, and presumably more adverse early life experiences, was reported to be associated with higher circulating levels of IL-6 (Carroll, Cohen, & Marsland, 2011); while a longitudinal study found that childhood maltreatment predicted risk for low-grade inflammation in adults (Danese, Pariante, Caspi, Taylor, & Poulton,

2007). Using an acute laboratory social evaluative stress test (Trier Social Stress Test – TSST) (Kirchbaum, Pirke, & Hellhammer, 1993), other researchers demonstrated that healthy adults exposed to childhood maltreatment exhibited a greater elevation in plasma IL-6, compared to those without a history of childhood maltreatment (Carpenter et al., 2010). Such a proinflammatory phenotype linked to early life adversity was shown to emerge during young adulthood, as peripheral blood mononuclear cells (PBMCs) derived from young women raised in a harsh family climate produced more IL-6 in response to *in vitro* challenge with lipopolysaccharide and in response to real-life psychological stressors (Chen et al., 2010; Miller & Chen, 2010).

Little is known about the effect of prior life stressors on psychological, neuroendocrine, and inflammatory responses of women who face the adaptive challenges inherent to pregnancy, along with the anticipation of impending role change and responsibilities associated with parenting. Evidence does support, however, that maternal psychological stressors and accompanying emotions—such as depression, anxiety, fatigue, and other mood disorders—influence infant short and long term health outcomes (Ruiz & Avant, 2005). Although the mechanism as to how this transpires is not clearly understood, results of animal and human studies suggest involvement of maternal-fetal stress response systems (Sandman, Davis, Buss, & Glynn, 2011a, 2011b). That evidence, although not consistent across studies, supports the theory that stress response hormones, like cortisol, may mediate the adverse effects of maternal psychosocial stressors on infant outcomes and future health (Diego et al., 2009; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004). Evidence derived from animal models of

prenatal stress response demonstrates prenatal stress exposure affects behavioral and biological development through activation of the HPA axis and its end product, the adrenal glucocorticoid hormone, cortisol (Coe et al., 2003; Maccari et al., 1996; Weinstock, 2005). Maternal stress response is associated with an increase in cortisol and corticotropin-releasing hormone (CRH) in the maternal-fetal dyad (Field et al., 2004; Weinstock, 2008), and this has been found to be associated with greater risk of preterm delivery and low birthweight infants (Diego et al., 2009). In addition, fetal exposure to elevations in cortisol is posited to result in impaired neurodevelopment. Compelling evidence supports a detrimental effect of cortisol on brain function, as increased cortisol exposure was found to change expression of a thousand genes in fetal cultured brain cells (Salaria et al., 2006). Also, elevated maternal prenatal cortisol was demonstrated to be associated with more negative infant behaviors (Davis et al., 2007). Recently, hair cortisol has been shown to be a reliable, non-invasive, retrospective measure of HPA axis activity (Russell, Koren, Rieder, & Van Uum, 2011). In a recent article, hair cortisol correlated with salivary samples in each trimester of pregnancy (D'Anna-Hernandez, 2011). Further, hair cortisol and salivary cortisol increased as gestation progressed, consistent with the known physiologic increase in cortisol over the latter part of pregnancy. While salivary cortisol has been used over the past decade to non-invasively measure cortisol, one of its limitations is that it reflects acute stress response, as opposed to chronic or cumulative stress response across pregnancy (D'Anna-Hernandez, 2011). Evaluation of chronic stress response biomarkers over larger time domains of pregnancy will provide critical insight as to the cumulative impact of stressors during pregnancy on

maternal-infant outcomes. The proposed study measures hair cortisol as an index of (HPA) activation as a retrospective marker, over a three-month time interval, as indicator of the stress response, during pregnancy.

The maintenance of a healthy pregnancy requires a shift in maternal cytokine balance toward an anti-inflammatory state (Reinhard, 1998); with more successful pregnancies there are higher circulating levels of the anti-inflammatory cytokine IL-10 (Jenkins, 2000; Lim, 1999). However, near term, in a normal pregnancy, a shift to an inflammatory state heralds the onset of labor and infant delivery. Atypical elevations in IL-6, IL-8, and TNF alpha, such as that which occurs with maternal infection, are linked to preterm birth (Gomez et al., 1995; Zhang, 2000). Important to this proposal, Coussons-Read and colleagues (2005) reported that women experiencing high levels of stressors during pregnancy have increased circulating levels of proinflammatory cytokines late in pregnancy compared to women not experiencing high levels of prenatal stressors (Coussons-Read, Okun, Schmitt, & Giese, 2005). Specifically, exposure to maternal prenatal stressors was associated with higher levels of the proinflammatory cytokines IL-6 and TNF-alpha and with low levels of the anti-inflammatory cytokine, IL-10 (Coussons-Read et al., 2005). More recently, this group evaluated associations between maternal psychosocial stress and cytokines during early, mid, and late pregnancy (Coussons-Read, Okun, & Nettles, 2007). That study showed that during both early and late pregnancy, higher levels of maternal stressors was related to elevations in circulating IL-6, while elevated CRP levels were associated with stressors during late pregnancy. Additionally, more prenatal stressors were related to lower serum IL-10 levels during

early pregnancy. In contrast, no associations were observed with stressors and circulating cytokines during the second trimester (Coussons-Read et al., 2007).

Significance

Prenatal stress-induced dysregulation of stress response hormones and cytokines may contribute to short-term and long-term effects on fetal and neonatal development (Entringer et al., 2010; Entringer, Buss, & Wadhwa, 2010). Because developing systems exhibit considerable plasticity, they are more easily affected by environmental stimuli, like maternal prenatal stressors (Hochberg et al., 2010). Disruption of the maternal-fetal neuroendocrine-immune milieu can adversely modulate developmental trajectories and affect biological, mental, and behavioral processes across the life span of the infant. It is anticipated that the results of this investigation will advance understanding of the influence of exposure to adverse life experiences during childhood on a woman's psychological, neuroendocrine, and proinflammatory response to her pregnancy. Also, results will provide insight as to whether maternal life experiences that occurred during her childhood relate to poor neonatal outcomes for her offspring. Such a determination has potential to positively impact maternal-infant health, by contributing to better identification of antenatal psychosocial risk that portends poor maternal-child health outcomes. The fetus is highly sensitive to the environment, and adverse experiences during critical periods of fetal development are known to increase life-long risk for disease (i.e., risk of cardiovascular, metabolic, and behavioral disorders) (Gluckman & Hanson, 2004). Thus the significance is magnified, as maternal prenatal stress response and exposure to stressors across pregnancy may result in life-long health issues for the

offspring. The findings from this study can provide the foundation for improved approaches to identify and stratify risk for adverse maternal-infant health outcomes, as well as guide the development of early intervention programs and health policy for women who are pregnant or who plan to become pregnant. This is significant because the well-being of mothers and infants determines the health of the next generation and is a priority of Healthy People 2020. Improving maternal-infant well-being can markedly reduce public health challenges and ultimately reduce health care costs over the lifespan (U.S. Department of Health and Human Services, 2011).

Conceptual Model

The model as depicted in Figure 1 illustrates potential linkages whereby maternal antenatal adverse experiences influence the mother's psychological well-being, neuroendocrine activity, and proinflammatory cytokine levels during pregnancy, ultimately affecting neonatal outcomes. For the purposes of this study, life adversity was conceptualized as a woman's pre-pregnancy exposure to adverse experiences, *prior to18 years of age*, originating from childhood and family experiences and/or related to low SES. Life adversity was measured by asking pregnant women to complete the Child Trauma Questionnaire (CTQ), which provides information on the woman's experience of adversity during her childhood. The experience of pregnancy is a normal life event; however, it is characterized by marked psychological, social, and physiological changes; a life change that for most women results in psychological stressors, requiring adaptation.

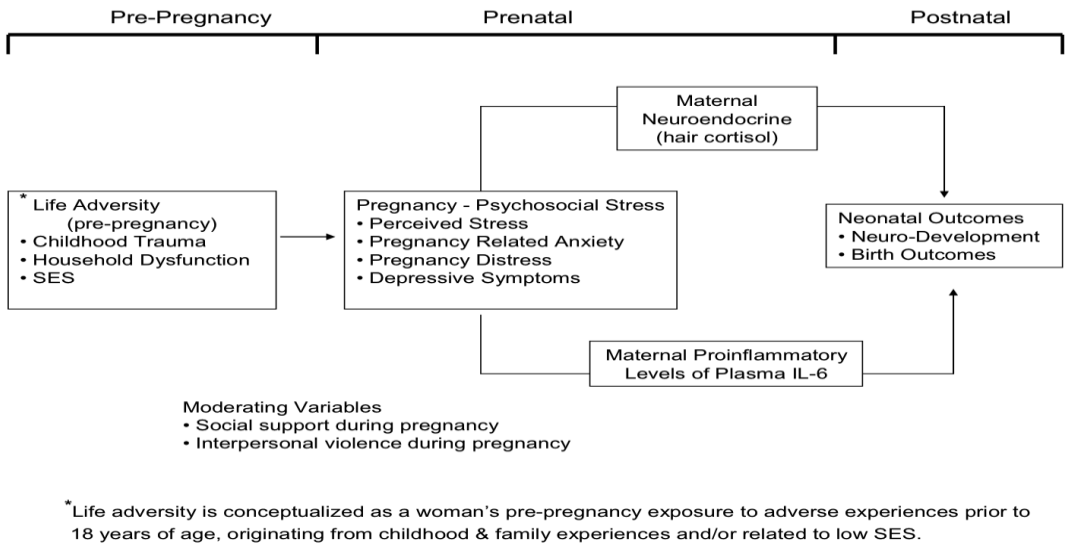


Figure 1. Life adversity: Impact on PNI profile during pregnancy and on neonatal outcomes.
(Note: Figure 1 describes posited linkages among study variables and is not intended to represent a path model.)

The proposed model posits that women who have experienced greater adverse experiences during their childhood will respond to their pregnancy, with greater stress perception (general distress), greater depressive risk, anxiety, mood disorder, and more sleep dysregulation. Additionally, greater childhood adversity will result in elevated neuroendocrine (cortisol) and proinflammatory (IL-6 and TNF-alpha) cytokine levels during pregnancy. This model is supported by evidence derived from animal and human studies that identify early life adversity as a vulnerability factor that gives rise to an adult phenotype characterized by a heightened stress reactivity. This heightened stress reactivity is characterized by greater psychological, cortisol, and proinflammatory responses to stressful life events (Entringer et al., 2008). It is further hypothesized that moderating factors (i.e., protective factor) will influence the effect of antenatal adversity.

Maternal moderating factors to be evaluated are levels of social support available to a woman during her pregnancy. Greater social support during pregnancy is posited to lessen (i.e., buffer) the impact of antenatal life adversity on outcomes. Lastly, the increased intensity of the woman's response to stressors across pregnancy (psychological, cortisol, TNF-alpha, and IL-6) was posited to result in worse neonatal outcomes (Entringer, Buss, Shirtcliff, et al., 2010; Entringer, Buss, & Wadhwa, 2010; Entringer et al., 2008). Further, the stress response during pregnancy is evaluated using perceptions of stress over a period of weeks to months while plasma blood analysis evaluates a static measure of inflammation in cytokines, and hair cortisol evaluates HPA activation across the last three months. The neonatal outcomes to be evaluated include birth weight and gestational age. While most studies focus on evaluating each individual stressor (perceived stress, depression, anxiety) across pregnancy, this study is unique in its innovative approach to create a Distress Composite Score using PCA to evaluate stressors during pregnancy—specifically, mid-pregnancy and late-pregnancy. This allows the researcher to better evaluate chronic stress through maternal child adversity, experienced in the first 18 years of life, with acute trauma experienced during current pregnancy.

CHAPTER TWO

REVIEW OF THE LITERATURE

Healthy People 2020 identified maternal-infant health as an important national health indicator, and thus a health priority for the nation (U.S. Department of Health and Human Services, 2011). Premature delivery, low birth weight (LBW) and infant mortality are key benchmarks for maternal-infant health status (U.S. Department of Health and Human Services, 2011). Premature and LBW infants have greater risk of negative neurodevelopmental outcomes. Additionally, premature as compared to term infants are at a greater risk for adverse psychological health, including depressive disorder, bipolar affective disorder, and non-affective psychosis (1.3, 2.7, and 1.6 times greater risk, respectively) (Nosarti et al., 2012). Adversity during childhood is increasingly recognized as a vulnerability factor for poor adult health. Yet, there is very little research investigating the psychological, neuroendocrine, and immune impact of childhood adversity during pregnancy on either maternal or neonatal outcomes. Adverse life experiences are associated with poverty (Hatton & Emerson, 2004), depressive symptoms, (Heim & Binder, 2011; Heim et al., 2010), and childhood psychiatric disorder (Hatton & Emerson, 2004), with the latter characterized by insecure attachment and social processing disorders. Moreover, significant life events prior to or during pregnancy enhance the likelihood of delivering a LBW infant (Khashan et al., 2008). Emerging

research suggests maternal life experiences may create a sub-optimal environment, affecting the fetus and altering development.

Premature and Low Birthweight Infant

In 2008 premature delivery accounted for 12.3% of all births in the United States, escalating health care costs (Mathews & MacDorman, 2010) (see Appendix A). For example, in 2005, premature births alone cost the US government an estimated $26 billion, with over $50,000 spent per child (Behrman & Butler, 2007). Expenditures exponentially increase when the cost associated with long-term care related to neurological, cognitive, and behavioral disorders is included (Talge, 2007).

While rates of premature delivery approach 13% for all women, rates for African American women (AAW) are over 17% for 2008 alone; and these rates remained virtually unchanged over the past two decades (2008 vital statistic data) (see Appendix B). These data suggest that AAW have a 60% greater risk for moderate preterm birth (28-37 weeks gestation) and a 2.5-times greater risk for extreme preterm birth (<28 weeks gestation) (Martin et al., 2009). Additionally, premature infant delivery rates for very low birth weight (VLBW) (<1500 grams) and low birth weight (LBW) (<2500 grams) are far greater among non-Hispanic Black women (2.5%, 11.6%, respectively) than for White (0.8%, 5.3%, respectively) and Hispanic women (1%, 5.7%, respectively) (Martin et al., 2010) (see Appendix C). This increase represents a 200% and a 120% increase, respectively, for VLBW and LBW infants in AAW as compared to White women (Martin et al., 2010). While premature birth rates have declined slightly in all races (2006-2008 data), there remains a gap in understanding why AAW continue to have the highest

proportion of premature birth rates despite access and improvements in prenatal health care.

Collins (Collins, Wu, & Davis, 2002) suggests that there is an intergenerational effect of poverty and a greater risk of LBW delivery among AAW in Cook County, IL (Collins, Rankin, & David, 2011; Collins et al., 2002). Additionally, another study noted an intergenerational decrease in birth weight among female descendants of non-US-born AAW in contrast to an increase in birth weight among descendants of European-born White women (Collins et al., 2002). Meanwhile, in another study, there were differences in birth weight when comparing the maternal birth weight to their offspring's birth weight in AAW as compared to Whites (Coutinho, 1997). This evidence suggests that the exposure to factors across generations, in addition to throughout gestation and childhood, may have a programming effect on the developing infant, resulting in intergenerational risk for LBW infants. These health disparities suggest there may be risk factors that are mediated by intergenerational or epidemiological links, which increase the incidence of premature and low birth weight delivery.

Biological Embedding

Adverse childhood experiences may be a risk factor in women during pregnancy that contributes to premature and LBW delivery and poor neurodevelopmental infant outcomes. This risk may arise from early life biological embedding that results in recalibration of stress response systems, which persists into adulthood (Hertzman, 1999). For pregnant women, early life adversity may dysregulate the dynamic balance of neuroendocrine-immune processes needed for optimal birth outcomes. Thus, it is

plausible that poor maternal-infant outcomes may emerge due to a dysregulated maternal neuroendocrine-immune profile consequent to exposure to early life adversity. Yet, there is little understanding of what psychosocial factors matter most and what underlying bio-behavioral mechanisms mediate the effects of early life adversity.

Compelling evidence suggests that the developing fetus is highly sensitive to his/her environment, which in essence is a reflection of the maternal environment. Environmental demands, such as that resulting from exposure to maternal stressors, are now known to alter malleable physiological systems and predispose not only to poor infant outcomes but also to poor health in adulthood. The sensing of the environment by the developing fetus results in an adjustment of physiologic set points and this is referred to as fetal programming (Davies & Norman, 2002; Welberg & Seckl, 2001). Initially adaptive, fetal programming in response to environmental demands imprints developing systems in a manner that shapes both the biological and behavioral phenotype; however, such phenotypic molding can also be maladaptive and predispose to disease later in life. The importance of fetal and infant health to adult health outcomes was first described by Dr. David Barker, whose studies demonstrated an association between low birth weight and increased systolic blood pressure (Barker, Bull, Osmond, & Simmonds, 1990; Barker, Osmond, & Law, 1989). Since that initial work, a multitude of studies have confirmed these early findings (Gluckman & Hanson, 2004), culminating in what is termed the Developmental Origins of Health and Disease (DOHaD) theory. According to DOHaD theory, an adverse intrauterine environment results in an integrated set of adaptive responses, which resets the developmental trajectory in anticipation of adverse

conditions to be encountered later in life. Mismatch between the anticipated postnatal environment and the reality of it exposes the organism to risk of adverse outcomes; the greater the mismatch, the greater the risk (Gluckman, Hanson, & Beedle, 2007).

The DOHaD offers a framework that emphasizes the importance of early perinatal life experiences on life-long risk for disease (i.e., risk of cardiovascular, metabolic, and behavioral disorders). Importantly, this applies to the maternal psychological milieu, as accruing evidence demonstrates that maternal psychological stressors, accompanied by maternal depression, anxiety, fatigue, and mood disorders can influence infant short- and long-term health outcomes (Ruiz & Avant, 2005). Although the mechanism is unclear, evidence suggests that this may occur as a consequence of activation of maternal-fetal stress response systems (Sandman et al., 2011a, 2011b) Maternal-fetal stress response activation alters levels of stress hormones that may, in turn, mediate the adverse effects of the maternal psychological state on infant outcomes and future health. As well, stress-induced dysregulation of the immune and inflammatory processes (i.e., proinflammatory cytokines) that are key to successful development and postnatal outcomes are also potential mediators of maternal stressors on fetal and neonatal development (Entringer, Buss, & Wadhwa, 2010; Wadhwa, Entringer, Buss, & Lu, 2011). Developing systems are especially vulnerable, as they exhibit considerable plasticity in response to environmental demands. Moreover, the window of developmental plasticity extends from preconception to early childhood and evolving research suggests that the mechanism likely involves epigenetic imprinting in response to environmental stimuli (Hochberg et al., 2010). As a result, early life cues set the trajectory for long-term biological, mental, and behavioral

responses that can persist across the life span. On the other hand, if effects of adverse early life experiences are mediated through epigenetic modifications, the outlook is not grim, as increasing evidence shows epigenetic states to be reversible. This opens up the opportunity for interventions during critical developmental windows, during both pre- and postnatal life (Gluckman, Hanson, & Mitchell, 2010). For instance, emerging evidence demonstrates promise for early life environmental enrichment to reverse epigenetic modifications consequent to adverse early life experiences (Branchi, Karpova, D'Andrea, Castren, & Alleva, 2011).

Given the important influence of the maternal psychological environment on infant and adult health outcomes, the purpose of this review is two-fold: (1) to establish the importance of investigating the impact of early maternal prenatal stressors on mother-infant health; and (2) to discuss potential mechanisms through which prenatal stress response impacts mother-infant health.

Psychoneuroimmunology Kopnisky (Kopnisky, Stoff, & Rausch, 2004) embraces an integrated approach to explain the influence of environmental demands on one's biology and behavior and how that impacts health via the immune system. With this purpose in mind, PNI theory, as a framework for understanding bio-behavioral processes that predict maternal-infant health, is reviewed. Next, key research studies that have evaluated the effects of maternal stressors—including anxiety and depression—on maternal-infant health are considered. Additionally, a brief identification of the current literature on prior life adversity during pregnancy is presented. Issues related to research design are addressed and recommendations for future studies are identified.

Psychoneuroimmunology: Theoretical Framework

PNI offers a theoretical framework to understand the integration of psychological and physiological factors and how psychosocial context influences maternal-infant health outcomes. PNI posits that a person's adaptive response to the environment involves coordinated interactions among the nervous, endocrine, and immune systems. For centuries, mind-body philosophy was rooted in anecdotal evidence. Then in 1980, the term *psychoneuroimmunology* was introduced by Robert Ader to denote the study of the interactions among behavioral, neural, and endocrine (neuroendocrine) systems with immunological processes of adaptation (Ader, 1980). This was in contrast to the prevailing view that the immune system operated autonomously from the brain (Maier, Watkins, & Fleshner, 1994). In the last 30 years strong evidence has accrued that establishes the existence of primary biological pathways linking the brain with the immune system (Maier et al., 1994; McEwen et al., 1997). These biological pathways are bi-directional, in that the brain not only influences immune function but products of the immune system (i.e., cytokines) can also signal the brain and influence the expression of behavior and emotions (Witek-Janusek, Tell Cooper, & Mathews, 2010) (see Appendix C). The connections among the brain and the cells and tissues of the immune system include direct innervation of lymphatic tissue and a shared communication grid in which cells of the nervous, endocrine, and immune systems use similar molecules and receptors to mutually affect behavior and physiologic function. Thoughts, emotions, and behavior are known to activate these pathways and in turn modulate immune function (Mathews & Janusek, 2011). This is consistent with the expanding body of evidence that supports the

role of emotions in the development and/or progression of disease (Irwin, 2008; Kemeny & Schedlowski, 2007; Witek-Janusek, & Mathews, 2012; Witek-Janusek, Tell Cooper, & Mathews, 2010; Wrona, 2006).

Brain and Immune System

The neuroendocrine system and autonomic nervous system (ANS) are two of the major biological pathways connecting behavioral events to the immune system. The immune system can be influenced by either the release of catecholamines through activation of the sympathetic division of the ANS, or of acetylcholine subsequent to activation of the parasympathetic division of the ANS. Further, sympathetic nerve terminals in immune organs connect with lymphocytes and have features much like synaptic junctions, suggesting the physical connection to the central nervous system (Maier et al., 1994). As a result, ANS stimulation can modulate immune function when environmental demands are perceived as a threat that provokes arousal and/or an emotional response. Because immune cells have adrenergic and cholinergic receptors, as well as receptors for other neurotransmitters, immune function can be altered in response to ANS activation. For example, stimulation of these receptors results in functional changes in immune response, including cytokine secretion, lymphocyte proliferation, natural killer cell cytotoxicity, and antibody production (Elenkov & Chrousos, 2006; Wrona, 2006). ANS activation does not solely produce immunosuppression, as originally thought. It is now realized that in response to ANS activation, certain aspects of the immune response may be stimulated whereas other responses are suppressed. This has

led to the current thinking that stressors produce immune dysregulation, especially if it is chronic (Calcagni & Elenkov, 2006; reviewed in (Witek-Janusek, & Mathews, 2012)).

A new view of the relationship between the immune system and the parasympathetic nervous system has recently emerged. Compelling research has established that vagal parasympathetic pathways suppress the release of proinflammatory cytokines and dampen inflammatory responses (Czura & Tracey, 2005; Thayer & Sternberg, 2010). Evidence demonstrates that greater vagal tone is associated with lower TNF-alpha and IL-6 (Marsland et al., 2007). It is now believed that this cholinergic anti-inflammatory pathway is a key adaptive mechanism by which the body reduces excess inflammatory responses to stressors (Elenkov, Iessoni, Daly, Harris, & Chrousous, 2005; Sternberg, 2006). Little, if any, research has evaluated the cholinergic anti-inflammatory pathway during pregnancy or during the postpartum period.

Neuro-Endocrine-Immune Connection

The hypothalamic-pituitary-adrenal (HPA) axis serves as an important neuroendocrine stress response system. Activation of the HPA axis occurs when a stressful event is experienced, causing the release of corticotrophin-releasing hormone (CRH) from the hypothalamus and the subsequent release of ACTH from the anterior pituitary (Maier et al., 1994). ACTH, in turn, causes the adrenal cortex to release cortisol, a glucocorticoid with strong immuno-modulatory effects. Cortisol is an anti-inflammatory stress response hormone; yet it also influences the overall balance of cytokines and is associated with pro-inflammatory effects. Cytokines are protein

molecules that regulate the immune response but also can signal the brain and influence behavior and emotional state; hence, cytokine balance is key to studies in PNI.

Lymphocytes that primarily secrete interferon (IFN) gamma, interleukin (IL)-2, and tumor necrosis factor (TNF) are classified as Th1 lymphocytes. These cells support cellular immunity. In contrast, lymphocytes that predominately secrete IL-4, IL-10, and IL-13 are classified as Th2 lymphocytes. These support humoral immunity (Elenkov & Chrousos, 1999; Mosmann & Sad, 1996). For the most part, under conditions of stress response activation, cortisol and catecholamines shift the cytokine balance toward greater levels of Th2 cytokines and reduced levels of Th1 cytokines. For example, glucocorticoids (i.e., cortisol), norepinephrine, and epinephrine suppress the production of IL-12 by antigen-presenting cells. IL-12 promotes a Th1 response to antigen and in its absence, a shift to a Th2 profile of cytokine production results. Furthermore, it is well established that stressors are accompanied by elevations in proinflammatory cytokines, such as IL-1, IL-6, and TNF-alpha. It is theorized that a key role of cortisol release during stress response activation is to attenuate the effects of proinflammatory cytokines and thus reduce the potential damage that can result from exaggerated or prolonged release of inflammatory molecules (Sternberg, 2006). For example, HPA axis dysregulation can occur under conditions of prolonged stress response, and cortisol becomes less effective in dampening stress-associated release of inflammatory molecules, like IL-6 (McEwen, 2000; G.E Miller, Cohen, & Ritchey, 2002). It is clear that the relationship among glucocorticoids, catecholamines, inflammation, and the immune system during stress response activation is complex, and dysregulation of these relationships can influence

health. It has become increasingly clear that when inflammation is not curtailed after a stress response, there is increased risk for inflammation-based disease like depressive illness or other affective and cognitive disorders (Dantzer & Kelley, 2007). For example, individuals with major depression demonstrate HPA axis dysregulation, which may be contributory to this affective disorder (Irwin & Miller, 2007). The role of stress-induced cytokine dysregulation during pregnancy has received little attention in the literature.

Cytokine to Brain Signaling

As noted above, a delicate balance between pro-inflammatory cytokines and anti-inflammatory cytokines is required to maintain homeostasis of the immune system. Cytokines are key molecules that signal the brain and modulate behavior. Moreover, extant research indicates that acute stress response modulates many aspects of immunity, which may not only contribute to disease but also contribute to behavioral disorders. (Cover & Irwin, 1994; M. Irwin, 2002; Irwin & A. Miller, 2007; Miller, 2009). Proinflammatory cytokines were first found to induce what was initially termed "sickness behavior," characterized by a constellation of symptoms, such as depressed mood, fatigue, lethargy, and disturbed sleep (Miller, 2009). Miller (2009) suggested that sickness behavior is an evolutionary protective response, causing the body to protectively shut down other activities and shift focus to aid healing. Yet, if excessive, proinflammatory cytokines can increase risk for depression (Miller, 2009). Capuron and Miller (2004) demonstrated that patients given the cytokine, interferon alpha (IFN-alpha), for medical treatment developed significantly higher rates of depression, which subsided following its discontinuation (Capuron & Miller, 2004). Cytokines contribute to sickness

behaviors like fatigue, sleep disruption, depressed mood, anxiety, impaired memory, and anhedonia by signaling the brain to induce central activation of the brain cytokine network (Capuron & Miller, 2004). Understanding the physiologic role of cytokines on psychological responses is critical to appreciate when caring for women who are undergoing prenatal and postnatal stressors; especially in light of the heightened risk for depression during the prenatal period. Factors influencing psycho-physiological responses may have greater negative effects on health when experienced in the context of pregnancy and the unique demands that pregnancy imposes on the mother and the developing fetus.

Maternal Prenatal Stressors and Health Outcomes in the Offspring: Overview

While the application of a PNI framework to maternal-child research is relatively new, it is highly relevant to an understanding of the impact of prenatal stressors on maternal-infant outcomes. For the pregnant woman, many factors can provoke both psychological and physiological stress, including unplanned pregnancy, teen pregnancy, chronic health conditions like diabetes, domestic violence, financial issues, lack of adequate social support, premature delivery, fertility issues, and previous pregnancy loss. Understanding how prenatal stress impacts mother-infant and future health is the focus of this review.

Fetal and neonatal exposure to maternal stressors is posited to exert a major (programming) influence on the trajectory of fetal and neonatal development, which has potential to alter health across the life span. While maternal exposure to teratogens during pregnancy is known to cause lethal defects, less is known about the effects of maternal

stress exposure on mother-infant health. Emerging work, however, implicates exposure to prenatal stressors as a contributing factor to adverse maternal-infant health outcomes, including increased risk for preterm delivery, intrauterine growth restriction, and impaired neurological, behavioral, and social-emotional development. The timing of fetal exposure to maternal psychological or biological stress is coupled with distinct profiles of birth outcomes, fetal/neonatal reactivity, and future health outcomes (Sandman et al., 2011a, 2011b). Effects of stressors on pregnancy outcomes may be attributed to stress-induced alterations of stress response activation of hormones and inflammatory molecules (i.e., cytokine dysregulation) (Coussons-Read et al., 2007; Ruiz & Avant, 2005). Given that the developing brain and body systems are more plastic or malleable compared to that of adults, the fetus is more vulnerable to the adverse effects of stressors, and these effects can imprint long-lasting changes through fetal programming (Bilbo, 2011). The concept of programming refers to the associations between environmental events (internal and external to the organism) and stable alterations in the phenotype of the offspring (Meaney, 2007).

Early life programming primes the fetus for adaptation to the extra-uterine environment; however, due to plasticity of developing systems in the early fetal and postnatal periods of life, maladaptive programming can also occur. For example, maternal exposure to stressors may precipitate maladaptive changes that alter the structure, function and biochemistry of the fetal brain and other developing tissues (Bilbo & Schwarz, 2009). Animal models establish that adverse early life environments—such as exposure to physical or psychological stressors, restricted or unbalanced nutrition,

alcohol or tobacco impaired utero-placental perfusion, and exposure to prenatal synthetic glucocorticoids—result in programming of developing physiological systems that can impair growth and development of the offspring. In particular, the developing HPA axis is highly susceptible to programming by early life events and this can alter life-long stress reactivity and future physical and mental health (Matthews, 2000; Matthews, Owen, Banjanin, & Andrews, 2002; Welberg & Seckl, 2001). Abnormal levels of cortisol resulting from maternal prenatal stress exposure during critical periods of development may mediate poor birth outcomes. For example, early exposure to prenatal maternal stressors with elevated cortisol levels early in gestation was shown to delay mental and motor development (Lupien et al., 2005; Field, 2011). In contrast, late exposure to elevated cortisol (with gradual increase of cortisol over time) is associated with enhanced mental performance (Davis & Sandman, 2010). Preterm birth is one potential outcome of fetal exposure to stressors during gestation; yet, there are other adverse outcomes that emerge during adulthood. Early life exposure to stressors can predispose to obesity, hypertension, cardiovascular disease, diabetes, and psychiatric disease in the offspring (Cottrell & Seckl, 2009). On the other hand, early life programming can have positive effects. For instance, maternal-infant interactions that are supportive and nurturing provide an environment that can enhance growth and development of the offspring, modulate HPA reactivity, reduce the risk for diseases or disorders in adulthood, and increase resiliency throughout life (Meaney, Szyf, Seckl, 2007). The biological mechanisms, which mediate the effect of early life programming, are under intense investigation. Promising lines of research indicate that this may involve epigenetic

processes (Gluckman & Hanson, 2004; Weaver, 2004). (Epigenetics refers to stable changes in DNA that occur in response to the environment but do not involve alterations to the DNA base pairs (Mathews, 2011).)

In fact, recent research shows differences in peripheral blood DNA methylation patterns in children who were institutionalized versus those raised by parents (Naumova et al., 2012). Also, findings recently showed childhood SES was associated more with an adult blood DNA methylation pattern than adult (current) SES (Borghol et al., 2012). These data translate findings from animal models to human paradigms, demonstrating that adverse early life experiences exert epigenetic modification, which persists into adulthood. The following discussion reviews the impact of prenatal stressors and the emotions (depression and anxiety) it engenders on neonatal and future health outcomes. In addition, potential biological pathways posited to mediate the effect of prenatal stressors are discussed.

Maternal Prenatal Stressors: Health Outcomes

Exposure to maternal prenatal stressors is not without consequence. Several prospective studies provide evidence that stressors experienced during pregnancy, including maternal anxiety or depression, are associated with adverse neonatal outcomes that influence future health, including risk for mental health disorders like attention deficit hyperactivity disorder (ADHD), autism, and schizophrenia (O'Donnell, 2009) (see Appendix D). The primary outcomes evaluated in studies of prenatal stressors include alterations in fetal/infant growth, abnormal social-emotional development, neurobehavioral impairments, and delayed cognitive development (Beydoun & Saftlas,

2008; Talge, 2007). The following will review major findings, commonalities, and inconsistencies among select studies, which have evaluated consequences of prenatal stress. This is followed by a consideration of potential psychobiological mechanisms proposed to mediate the adverse outcomes of maternal prenatal stressors.

Neonatal Outcomes: Birthweight and Prematurity

A body of evidence suggests that maternal prenatal stressors—including daily hassles, depression, anxiety, and the experience of negative life events during pregnancy—result in earlier delivery and smaller birth weight (Talge, 2007). For example, women with scores on the Center for Epidemiological Studies Depression tool CES-D (Radloff, 1977) greater than or equal to16 (cut score for depression risk) were found to have nearly twice the risk for preterm delivery. Further, this risk escalated with increasing severity of depression and was independent of antidepressant medication (Li, 2009). Prenatal anxiety also increases the incidence of premature delivery and low infant birth weight. One study showed that women with prenatal anxiety have higher rates of prematurity and lower birth weights, as compared to women with prenatal depression (i.e., 10% as compared with 6.5%, respectively) (Field, Diego, Hernandez-Reif, Figueiredo, Deeds, Ascencio, Schanberg, & Kuhn, 2010). These results were confirmed by a large population-based study (N=3,000), which found that maternal anxiety and depression predicted both premature birth (OR=1.16) and low birth weight (OR=1.08) (Cooper, Murray, Hooper, & West, 1996). Thus, both prenatal anxiety and depression are important psychological factors that influence prematurity and birth weight of offspring.

Similarly, pregnancy-specific anxiety was found to result in a two-fold increased risk of premature delivery, while perceptions of racial discrimination increased risk for premature delivery (RR=1.4) (Dole, 2003). Further, greater negative life events, combined with pregnancy-specific anxiety, increased the relative risk of premature birth (from OR 2.1 to 2.6) (Dole, 2003); while greater maternal perception of negative life events during pregnancy increased the odds (OR 1.8) of preterm birth, independently of obstetric complications and maternal substance abuse (Dole, 2003). Acute exposure to traumatic events was also shown to reduce infant birth weight and shorten gestation (Harville, Xiong, & Buekens, 2010 2010). For instance, pregnant women in the vicinity of the Word Trade Center terrorist attack (9/11) delivered infants with a birth weight below the 10th percentile (OR=1.90) (Berkowitz et al., 2003).

More recently, a meta-analysis evaluated psychosocial stressors and perinatal outcomes. That analysis evaluated 35 studies (N=31,323 women) which met inclusion criteria (based on rigor of design). Findings demonstrated that exposure to psychosocial stressors during pregnancy was significantly associated with risk for low birth weight; but this association, although significant, was very small. The authors concluded that other lifestyle variables and/or risk factors (i.e., vulnerability factors) need to be considered in combination with measures of psychosocial stressors to fully address the role of prenatal stressors on prematurity and birth weight (Littleton, Bye, Buck, & Amacker, 2010 & Amacker, 2010). It is also noteworthy, that a variety of tools are used by investigators to evaluate psychosocial stressors; including total number of stressful life events, daily

hassles or minor stressful events, perceived stress, and adverse life events (Littleton, Bye, Buck, & Amacker, 2010).

Neuro-Developmental Outcomes

A large number of studies have demonstrated that exposure to maternal antenatal stressors results in a variety of effects that adversely impact the neurobehavioral, social-emotional, and cognitive function of offspring. Although these human studies do not provide causal evidence, the findings are consistent across studies and the effects are buttressed by results obtained from experimental animal models that do indeed demonstrate causality (see Appendix D). What is remarkable about these studies is that they demonstrate that adverse outcomes result from diverse stressor types and intensity, ranging from trauma exposure (i.e., natural disasters) to minor stressors, like daily hassles (see Appendix D). Collectively, these results indicate that offspring of mothers with exposure to antenatal stressors are more likely to be afflicted with emotional disorders, including greater risk for attention deficit/hyperactivity, anxiety, delay in language development, autism, and schizophrenia (O'Donnell, 2009). Importantly, the magnitude of the adverse effects of prenatal stressors are considered to be clinically significant, as the attributable development of emotional/behavioral problems is estimated at roughly 15% (Talge, 2007). Furthermore, collective evaluation of this literature suggests that these effects are independent of effects related to maternal postnatal depression and anxiety (Talge, 2007).

The influence of postnatal confounds, like poor mother-child interactions in women who suffered from exposure to prenatal stressors, are an important design

concern, as many human studies have not controlled for influences of the postnatal environment on child development. The vast majority of studies have focused on the emotional reaction to the stressors accompanying pregnancy, namely maternal depression and anxiety. In light of this, the following provides a review of select studies that have evaluated prenatal maternal depression and anxiety.

Prenatal Depression

Prenatal major and minor depressive disorders are common during pregnancy. A recent review reports the incidence of prenatal depression to range widely, from 6% to 38% (Field, 2011). This wide range is related to a lack of distinction between clinical depression, as compared to depressive symptoms, the latter being more prevalent. For example, the incidence of prenatal depressive symptoms in the USA was reported to occur in 38% of pregnancies (Records & Rice, 2007). In contrast, a recent evaluation of a large sample of community women (N=1997) found that 5.1% of the sample reported antenatal clinical depression (clinical depression was defined using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria) (Gavin et al., 2011). Also, a prospective evaluation of an urban sample (N=1888) of pregnant women found that antenatal depressive disorders were present in 9.9%, with 5.1% meeting criteria for probable major depression and 4.8% meeting criteria for probable minor depression (Melville, Galvin, Guo, Fan, & Kanton, 2010). It is even likely that the prevalence of maternal prenatal depression is higher, as many cases go unreported. It is estimated that over 85% of women with depression and depressive symptoms go untreated. For example, in a large study (n=3472), 20% of pregnant women had CES-D scores >13 with

nearly 14% of this sample being untreated for depression (Marcus, Flynn, Blow, & Barry, 2003). This may, in part, be due to the prevailing notion among certain health care providers and the general public that depression is a "normal" part of pregnancy. Clearly, these statistics highlight not only the magnitude of this problem (Marcus, 2003, Blow, & Barry, 2003) but also the need to have conceptual clarity regarding the definition and measurement of depression versus depressive symptoms.

Investigators have identified many factors which influence risk for prenatal depression, especially race/ethnicity. One study identified Blacks and Asian/Pacific Islanders to be at greater risk for depression during pregnancy, compared to non-Hispanic White women; this persisted even after controlling for a number of other risk factors (Gavin et al., 2011). Another study confirmed greater risk of prenatal depression for African American and Asian women, but also found that Hispanic race independently increased risk for any type of depression (Melville et al., 2010). That study, which sampled urban women, also found that psychosocial stressors, domestic violence, and chronic medical conditions increased the odds for prenatal depression; whereas older age decreased depressive risk. Others identified lower education, greater exposure to stressors related to fetal well-being and health, and severe marital conflict to be some of the strongest predictors of prenatal depression; followed by psychiatric or psychological history, stressors related to difficulties at work, and having a previous child with major or minor birth defects (Dayan et al., 2010). Further, findings from a recent study showed that factors which increased the odds of depression included psychosocial stressors, domestic violence, chronic medical health issues, and race; whereas advanced maternal

age decreased the odds of depression (Melville et al., 2010). In contrast, supportive relationships and marriage are associated with lower risk for maternal prenatal depressive symptoms. However, it should be noted that marriage must be qualified, as marital dissatisfaction is associated with greater depressive symptoms (Marcus, Flynn, Blow, & Barry,, 2003). Different risk factors predict major versus minor depression. Marchesi et al. (2009) found that prior depressive episodes and conflicts with husband/partner predicted major prenatal depression; whereas minor depression was predicted by being a housewife (i.e., no job outside the home), the presence of prior depressive episodes, and whether the pregnancy was wanted (Marchesi, Bertoni, & Maggini, 2009). Understanding risk factors for prenatal depression can lead to earlier identification and prevention of poor neonatal outcomes.

Investigators identify maternal depression during pregnancy to be associated with prematurity and low birth weight infants. This was recently substantiated by findings from a multi-international meta-analysis, which documented that antenatal depression associated with premature birth and low birth weight delivery (Grote et al., 2010). Additionally, when using a categorical measurement for antenatal depression, major depression or clinically significant symptoms of depression increased the relative risk of premature birth, low birth weight, and IUGR by 39%, 49%, and 45% respectively (Grote et al., 2010). Moreover, this meta-analysis identified the following most significant variables to control: smoking or substance abuse, race or SES, history of preterm delivery, and antidepressant treatment with a serotonin uptake inhibitor (SSRI).

Substantial evidence demonstrates that maternal prenatal depression negatively impacts the neurobehavioral outcomes for the offspring. In general, prenatal depression is linked to excessive infant activity, fetal growth delay, prematurity, low birth weight, disorganized sleep, and neonatal reduced responsiveness to stimuli (Field, 2011). Effects of prenatal depression can be initially observed in the fetus, as prenatal depression together with prenatal anxiety was shown to result in greater fetal activity, explaining 39% of the variance in infant activity (Dieter et al., 2001). In response to vestibular stimuli, however, the fetuses of prenatal depressed women showed less total movement and an increase in heart rate, as opposed to a decrease in heart rate (a decrease in heart rate is normally associated with attention to stimuli) (Emory & Dieter, 2006).

In the early neonatal period prenatal depression may interfere with maternal-infant interactions. Mothers with prenatal depression more often perceive their infant's temperament as difficult, as compared to non-depressed mothers (McGrath, Records, & Rice, 2008). In a large study investigating term infants, mothers with prenatal depression in the third trimester had greater perceptions of negative infant behaviors and higher levels of cortisol, even when maternal psychological measures were controlled. In that study, perceived stress did not predict maternal perceptions of infant temperament (Davis et al., 2007). In contrast, however, Pesonen and colleagues (2005) did find that prenatal maternal stressors predicted a greater maternal perception of negative infant temperament (Pesonen, Raikkonen, Strandberg, & Jarvenpaa, 2005). Of note, maternal subjective report of infant temperament should be complemented with objective measures or observations of the infant in order to increase measurement validity. This is particularly

important, as maternal postnatal affect will likely influence the mother's perception of her infant's behavior; albeit maternal perception is recognized as an important adjunct to objective observations of neonatal behavior.

The effects of prenatal depression extend beyond infant temperament, as these infants show attention, emotional, and behavioral problems that extend into childhood and influence future health (Field, 2011). Regarding attention, infants of depressed mothers exhibit greater arousal and less attentiveness to face/voice stimuli, as assessed by the Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Hernandez-Reif, Field, Diego, & Ruddock, 2006 & Ruddock, 2006). This is attributed to delayed attention and/or slower processing (Field, 2011). Also, older infants (3-6 months of age) were found to exhibit less negative responses to viewing their mother's non-contingent and still-face behavior. The authors interpreted this to indicate that these infants were more accustomed to this behavior in their mothers, suggesting that prenatal depressed mothers exhibit inferior interaction styles with their infants (Field, Diego & Hernandez-Reif, 2009). This was confirmed by other studies showing that these mothers spent less time smiling, touching, and imitating their infants (Field, Diego & Hernandez-Reif, 2009). Such findings emphasize the fact that postnatal maternal-infant interactions contribute to or synergize with the effects attributed to prenatal depression; certainly postnatal mother-infant interactions need to be controlled in studies evaluating the outcomes of prenatal stress exposure.

Mothers who have experienced prenatal depression more often have infants with sleep problems (Diego, Field, & Hernandez-Reif, 2005), manifested by their infants

spending less time in deep sleep and more time in disorganized sleep (Field et al., 2007). These infants are often perceived as being fussier and spending more time crying. This adds to maternal postpartum sleep inadequacy and exacerbates stressors experienced, such as fatigue and negative affect; all of which may further disturb maternal-infant interactions. Thus, a cycle that intensifies maternal negative affect results from infant sleep disturbance. Moreover, sleep disturbance often continues into childhood, as manifested by refusal to go to bed, waking up early, experiencing nightmares, and sleeping only for short intervals (O'Connor et al., 2007). Sleep problems are not benign, as infant sleep problems have been associated with childhood behavioral depression (O'Connor et al., 2007) and ADHD (Wiggs & Stores, 2005; Gruber, 2000 #1945;Stores, 2001 #2615)(Glover, 2011) This continues to be consistent in more recent literature with the exploration of maternal cortisol and cortisol levels in amniotic fluid during pregnancy is strongly correlated between the fetus and mother, particularly in those women with greater anxiety (Glover, Bergman, Sarkar, & O'Connor, 2009).

Many studies have established that male infants are at greater risk for poor neuro-developmental outcomes due to exposure to antenatal stressors. For example, a recent prospective case-control study evaluated the effect of prenatal depression (DSM-IV criteria) on neuro-development in one-year-old infants using the NBAS, and social emotional development using the Infant-Toddler Social and Emotional Assessment Scale. Prenatal depression was identified in 34 women and infant outcomes were compared to a non-depressed group (N=79). Findings revealed prenatal depression to be highly correlated with anxiety and stress response scores, suggesting that these affective states

accompany one another. Interestingly, the results demonstrated that male newborns of mothers with prenatal depression had lower scores than control infants on the motor skills and regulation of states based on the NBAS. Moreover, at one year of age, infants of antenatal depressed mothers exhibited more generalized anxiety, which again was more marked in males. Also the infants of prenatal depressed mothers scored higher on activity/impulsivity and had more sleep problems than infants of non-depressed mothers (Gerardin et al., 2011).

Prenatal Anxiety

Anxiety can be conceptualized as an emotional reaction to real or imagined stressor (Austin & Leader, 2000). Evidence suggests that prenatal anxiety has unique influences on fetal development and infant/childhood outcomes. This is especially the case when the anxiety is "pregnancy-specific anxiety"—that is, anxiety associated with worry about delivery or worry about fetal health, including infant disability (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010). A meta-analysis found that pregnancy-specific anxiety symptoms were associated with a lower infant gestational age. However, the effect size was small and the variance was large (Littleton, Breitkopf, & Berenson, 2007). Possible reasons for this variation in results may relate to other correlates of anxiety, including depressive symptoms, social support, negative life events (recent), perceived stress, optimism, and self-esteem (Littleton, Breitkopf, & Berenson, 2007). In another review of ten studies, gestational age and small for gestational age were not found to be associated with higher levels of anxiety (Andersgaard et al., 2008). In

contrast, when comparing second trimester high versus low anxiety, Field (Field et al., 2003) found high anxiety resulted in significant differences in birth weight.

Findings from a study of prenatal anxiety and infant outcomes suggest that maternal sensitivity to infant distress moderates the relationship between maternal prenatal anxiety and infant cognitive development. However, it failed to moderate the relationship between prenatal anxiety and infant psychomotor development when the infants were evaluated at seven months of age. These findings were independent of prenatal depression or combined postnatal depression and anxiety (Grant, McMahon, Reilly, & Austin, 2010 & Austin, 2010). Research also indicates that timing of exposure to anxiety may produce unique effects on fetal development (Grant et al., 2010). For example, early exposure to prenatal anxiety was independently associated with reduced scores on the Bayley Scales of Infant Development (BSID) at one year of age (Davis & Sandman, 2010). In contrast, late exposure to prenatal anxiety was associated with behavioral and emotional problems in boys and girls and hyperactivity with inattention in boys (O'Connor, Heron, Golding, Beveridge, & Glover, 2002 Beveridge, & Glover, 2002). Differences in developmental and behavioral outcomes based on timing of exposure likely occur because different brain regions develop at specific times during gestation, resulting in different windows of vulnerability.

Previous research shows that prenatal anxiety results in physiological effects on the infant. For example, infants of mothers who experienced prenatal anxiety appear to have impaired immune function, as they experience more infectious illness and require more frequent use of antibiotics throughout their first year (Beijers et al., 2010). Also,

infants born of mothers with anxiety during pregnancy have greater sleep disturbance. The effect on sleep was long lasting, as prenatal anxiety and depression each predicted greater sleep disturbance in infants at 1.5 and 2.5 years old (O'Connor et al., 2007). Infant sleep disturbance is posited to predict future behavioral problems or altered stress reactivity later in life. In support of this concept, it has been shown that infants born to mothers with prenatal anxiety exhibit elevated cortisol levels during childhood (O'Connor, Ben-Shlomo, Heron, Golding, Adams, Glover, 2005).

Prenatal Combined Depression and Anxiety

Anxiety often accompanies prenatal depression. Research by Field (Field, Diego, Hernandez-Reif, Figueiredo, Deeds, Ascencio, Schanberg, & Kuhn, 2010) identified greater developmental and socio-emotional problems in infants born to women who experienced both depression and anxiety during the prenatal period. For example, infants of mothers with combined prenatal anxiety and depression were found to spend less time in awake and alert states than infants of mothers without depression or anxiety (Diego et al., 2005). This may interfere with mother-infant bonding. Others show the combined presence of prenatal anxiety and depression predicted 27% and 20% of the variance in infant behavioral reactivity measured at four and nine months, respectively (Davis et al., 2004). The detrimental effects of combined prenatal anxiety and depression extend to childhood, as manifested by an association with greater symptoms of ADHD in children eight and nine years old (Van den Bergh & Marcoen, 2004), behavioral problems at four and seven years of age (O'Connor, Heron, Golding, Glover, & ALSPAC Study Team,

2003 Glover, & Team, 2003), and childhood anxiety and depression at 10 years of age (Leech, 2006 & Day, 2006).

Because anxiety and depression are highly correlated and produce similar effects (Davis, Glynn, Waffarn, & Sandman, 2011), it makes it difficult to disentangle the independent effects of depression versus anxiety (Field et al., 2011). Nevertheless, it is clear that mothers with both prenatal depression and prenatal anxiety represent a highly vulnerable group (T. Field, Diego, M., Hernandez-Reif, M., Figueiredo, B., Deeds, O., Ascencio, A., Schanberg, S., & Kuhn, C., 2010). Furthermore, the effects of and the linkages between prenatal anxiety and depression emphasize the importance of measuring not only perceived stress, but the emotional response to stressors, including both anxiety and depression.

Sleep Disturbance

Sleep disturbance is common during pregnancy and may escalate in response to maternal stress; yet sleep disturbance may also be a symptom of maternal depression. Either way, sleep disturbance is associated with psychological distress, including depression, anxiety, and mood disturbance (O'Connor et al., 2007). For example, prenatal sleep disruption in the second and third trimester is greater in women with depression or anxiety, or the combination of both depression and anxiety, as compared to women without depression (Field, Diego, & Hernandez-Reif, 2010; Field, Diego, Hernandez-Reif, Figueiredo, Deeds, Ascencio, Schanberg, & Kuhn, 2010). Further, prenatal sleep disruption in low SES AAW is greater in women with depression as compared to women without depression (Field et al., 2009). Hence, sleep disturbance is a key factor that can

moderate and possibly compound the adverse effects of prenatal stressors and negative mood states.

Sleep disruption is also known to alter immune function, HPA axis regulation, cortisol, and stress reactivity (Vera et al., 2009). During pregnancy, sleep disturbance may adversely alter critical aspects of immune function, such as cytokine regulation, leading to poor pregnancy outcomes (Okun, Hall, & Coussons-Read, 2007). Prior research shows that third trimester sleep disruption is associated with increased levels of the pro-inflammatory cytokine, IL-6 (Okun & Coussons-Read, 2007; Okun et al., 2007). In contrast, others report no effects of third trimester sleep disruption on IL-6 levels (Okun et al., 2007). The authors attribute this discrepancy to the wide variability in time that the samples were drawn from, the lack of consideration of the diurnal IL-6 rhythm (Dimitrov et al., 2006), and the lack of control for body mass index (BMI) (i.e., adipose tissue is a source of circulating IL-6) (Mohamed-Ali et al., 1997).

Maternal Prenatal Stressors: Biological Mechanisms

Activation of the maternal HPA axis and the resultant increase in circulating cortisol has been identified as a key biological pathway contributing to the detrimental effects of prenatal stressors on the developing fetus. Strong evidence for this proposition has been obtained from animal studies (O'Donnell, 2009 #1963;Talge, 2007 #1599). Yet the design and interpretation of studies in humans, which evaluate maternal HPA axis activation and cortisol as a mediating pathway for the effects of prenatal stress, is fraught with many complexities. Namely, the maternal HPA axis behaves differently as gestation progresses. Also, the placenta controls transfer of circulating products from mother to

fetus, and, furthermore, the fetal adrenal contributes to cortisol secretion. In the next section the evidence for cortisol as a mediating hormone for adverse effects of maternal prenatal stress on infant outcomes is considered.

Pregnancy and the HPA Stress Response System

During pregnancy, stress response systems undergo remarkable change to accommodate the developing fetus (Davis & Sandman, 2010). Overall, there is an increased secretion of the maternal and placental stress hormones that are necessary for maternal adaptation and fetal development. The placenta is central to the variations in stress hormones across pregnancy, as it expresses the genes for CRH and proopiomelanocortin, the precursor for ACTH and beta-endorphin; and all of these stress hormones gradually increase as pregnancy proceeds. Most dramatic, however, is the marked increase in CRH in maternal plasma, which attains levels comparable to that observed in the hypothalamic portal system during physical stress. As a result, some consider pregnancy itself to be a stressor (Lowry, 1993). During pregnancy, the elevated CRH levels are maintained by a positive feedback loop in which cortisol stimulates CRH production by the placenta. This results in elevations in ACTH, beta endorphin, and cortisol as pregnancy advances (Petraglia, Fiorio, Nappi, & Gennazzani, 1996; Robinson, Emanuel, Frim, & Majzoub, 1988). Yet by term, this positive feedback loop is blunted because maternal receptors for stress hormones become down-regulated. As a result, during late gestation environmental stress is less effective in triggering the HPA axis; thus, women become less responsive to stressors (Glenn, 2010; Glenn, Wadhwa, Dunkel-

Schetter, Chicz-Demet, & Sandman, 2001; Schuetze & Das Eiden, 2005) (see Appendix G).

Due to the influence of estrogen, maternal plasma corticosteroid binding globulin (CBG) levels increase progressively with advancing gestation until 36 gestational weeks when the CBG levels diminish (Ho, Lewis, & O'Loughlin, 2007). Changes in CBG influence the levels of biologically active cortisol during pregnancy. When cortisol is bound by CBG it is inactive, yet uncoupling of circulating cortisol from CBG provides a ready source for biologically active cortisol, if needed. Variations in CBG may be a factor in poor infant outcomes because lower levels of maternal prenatal CBG (i.e., greater biologically active cortisol) associate with fetal growth restriction (Ho et al., 2007).

In animal models during pregnancy, stress exposure, glucocorticoid exposure, and the blocking of placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) cause lower birthweight, greater blood pressure, and greater glucose levels (Seckl & Holmes, 2007). Further, the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) changes cortisol to its inactive form. Of importance to the fetus, maternal stress is known to also down-regulate placental 11β-HSD2, allowing for a greater proportion of maternal cortisol to cross the placenta and influence fetal development in adverse ways (Mairesse et al., 2007). This may alter fetal programming of developing tissues and could account for adverse effects of prenatal stress on maternal-infant health.

Maternal Prenatal Stressors: Neuroendocrine Mechanisms

Ample evidence derived from animal models of prenatal stress demonstrate that prenatal stress exposure affects behavioral and biological development through activation of the HPA axis, and in particular its end product, the adrenal glucocorticoid hormone (i.e., cortisol in humans and primates) (Coe et al., 2003; Maccari et al., 1996; Weinstock, 2005). It is clear that in response to maternal stress the fetal hormonal environment is altered. Maternal stress is associated with an increase in cortisol and CRH in the maternal-infant dyad (Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004; Weinstock, 2008), increasing risk for adverse infant outcomes.

The work of Field has shown that the fetuses of depressed women with increased prenatal cortisol exhibit growth retardation and these women deliver more preterm and low birth weight infants (Diego et al., 2009). Elevated evening cortisol and flattened diurnal rhythm of cortisol in the later part of pregnancy has also been associated with more infant illness (Beijers et al., 2010). Moreover, fetal exposure to elevations in cortisol is posited to result in impaired neurodevelopment. Compelling findings demonstrate increased cortisol exposure results in a change in expression of a thousand genes in fetal cultured brain cells (Salaria et al., 2006). Also supportive of cortisol's effect on fetal brain development are studies of infant neuro-behavioral outcomes that find elevated maternal prenatal cortisol to be associated with maternal reports of infant negative behaviors (Davis et al., 2007). This outcome was confirmed with investigator-observed negative infant behaviors at five months of age (de Weerth, van Hees, & Buitelaar, 2003). Additionally, elevated cortisol levels in later pregnancy were shown to

result in greater motor activity in infants, with boys being more vulnerable than girls (DiPietro, Kivlighan, Costigan, & Laudenslager, 2009). Others also showed that in an evaluation of 17 mother-infant pairs, 4 of 15 behaviors of young infants during everyday routines were correlated with maternal saliva cortisol during pregnancy (de Weerth, van Hees, & Buitelaar, 2003). Moreover, higher levels of maternal cortisol in the third trimester were found to be associated with more infant crying, fussiness, and negative facial expressions (Pfeifer, 2002). Long-term associations of prenatal cortisol are also linked to emotional disorders in childhood (depression and anxiety) and attention deficits/hyperactivity and delayed language development (Talge, 2007).

Prenatal stress has been shown to result in greater neonatal cortisol levels and this may also contribute to poor outcomes. Field and colleagues reported that maternal prenatal depression is directly correlated to cortisol levels in the infant (Field, 2011; Field, Diego, & Hernandez-Reif, 2010). Moreover, the combined effects of prenatal depression and anxiety resulted in greater levels of neonatal cortisol (as well as increased epinephrine and lower levels of dopamine and serotonin) compared to neonates of mothers with prenatal anxiety alone or to control women (Field, Diego, Hernandez-Reif, Figueiredo, Deeds, Ascencio, Schanberg, & Kuhn, 2010). Mothers with prenatal depression that exhibit higher cortisol, lower dopamine, and lower serotonin levels also showed alterations in biochemical markers in their neonates (Field et al., 2004; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004). Further, in a path analysis, prenatal cortisol mediated the relationship between antenatal depression and neonatal outcomes including prematurity; while prenatal norepinephrine mediated

the relationship between antenatal depression and infant low birth-weight (Field et al., 2004; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004). Additionally, in a later study, antenatal depression was associated with increased incidence of premature delivery and LBW (OR 2.6, 4.75, respectively) (Diego et al., 2009). Further, maternal CESD scores during pregnancy mediated the relationship among maternal antenatal second trimester cortisol levels, gestational age, and fetal growth rate, predicting 30% and 14% of the variance, respectively (Diego et al., 2009).

Yet the relationship of maternal stress-induced elevations in cortisol to fetal elevations in cortisol is complex and many unresolved issues remain. For example, as noted earlier, maternal cortisol responses to stress decline over the course of gestation, and earlier in pregnancy, the association between maternal and fetal cortisol is less robust. In contrast to studies linking maternal prenatal stress and cortisol to infant outcomes, others find no such relationships. For example, a study of women awaiting amniocentesis found no relationship between cortisol and trait anxiety and only a modest relationship was observed with state anxiety, in spite of these women reporting high anxiety levels (Bergman, Sarkar, Glover, & O'Connor, 2010). This same group also found no association between state anxiety and amniotic fluid cortisol (measured at one time point) and fear reactivity in infants at 17 months of age. Yet this study is limited by sampling women only at one point in time during pregnancy, examining them during an acute situational stress, and determining cortisol in amniotic fluid. Of note, the linkage of amniotic fluid cortisol to circulating (maternal and fetal) cortisol is not clear.

Nevertheless, these authors suggest that an HPA-mediated link between maternal and fetal cortisol is weaker or more complex than has been assumed.

This complexity is confirmed by other human studies, which do not support a simple relationship among prenatal maternal stress, cortisol, and child outcomes. For example, Davis et al. (Davis et al., 2007) found that maternal prenatal salivary cortisol predicted maternal reported infant temperament independently of prenatal stress. Also, a more recent evaluation of 81 women with normal pregnancies showed that prenatal general distress did not impact maternal cortisol levels after awakening (area under the curve) nor did maternal prenatal perceived stress correlate with infant size at birth. However, that study did find that newborns of mothers with higher prenatal salivary cortisol levels upon awakening (cortisol awakening response) had lower birth weights and were shorter at birth. In that study, maternal prenatal cortisol levels explained 19.8% of the variance in newborn birth weight and 9% of the variance in their body length, even after controlling for gestational age, parity, pre-pregnancy BMI, smoking, and infant sex. The authors concluded that maternal cortisol levels in pregnancy influence intrauterine growth and may be a better predictor for birth outcome than prenatal perceived stress (Bolten et al., 2011).

It is also possible that chronic stress might be more important than acute situational stress in elevating maternal/fetal cortisol and in producing untoward birth outcomes. It is known that chronic stress disturbs diurnal cortisol rhythms; yet few studies have evaluated diurnal cortisol in women with prenatal stress, depression, or anxiety. One study did find that women who had experienced a major life event or who

had high levels of pregnancy-specific anxiety exhibited higher evening cortisol, late in pregnancy (Obel et al., 2005). Another study also evaluated women during late pregnancy and found that those with high-trait anxiety had a flattened afternoon decline in cortisol, consistent with elevated afternoon levels (Kivlighan, DiPietro, Costigan, & Laudenslager, 2008). Others also evaluated maternal trait anxiety and found that maternal trait anxiety was associated with all stress-related psychological measures and that high-trait anxiety predicted low baseline cortisol awakening levels in early pregnancy. Thus, these results suggest that in addition to more thoroughly evaluating the HPA axis across the day, maternal prenatal trait psychological constructs also need to be considered together with state specific measures of stress, mood, and anxiety (Entringer, Kumsta, Hellhammer, Wadhwa, & Wust, 2009; Pluess, 2010).

In humans, however, elevations in maternal glucocorticoids are largely prevented from reaching the fetus through inactivation by placental 11β-HSD or by binding to CBG. Thus, some are skeptical as to whether maternal glucocorticoids mediate the effects of stress on the fetus. Yet there is evidence that prolonged or chronic maternal stress impairs feedback regulation of the HPA axis, resulting in elevations in cortisol. It is thus hypothesized that chronic stress-induced elevations in cortisol then increase the release of CRH from the placenta (via positive feedback). CRF can pass through the placenta and normally CRH initiates labor by stimulating the release of prostaglandins and oxytocin from the placenta (Florio et al., 2002). Studies show that increased plasma CRH predicts risk for preterm birth and low birth weight. Moreover, CRF has been implicated in preterm labor, reduced birth weight, and slow growth rate in prenatally stressed infants

(Inder et al., 2001; Ruiz, Fullerton, Brown, & Dudley, 2002; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, Sandman, 1996). For example, the incidence of preterm births was found to increase with a doubling of plasma levels of CRH (Weinstock, 2005). Greater levels of maternal CRH can stimulate the fetal adrenal and excess fetal cortisol is believed to disturb brain development and predispose to cognitive and behavioral disorders (Weinstock, 2005). These findings emphasize that chronic or enduring stress during pregnancy is more important than acute episodic stress (O'Connor et al., 2002; Stott, 1973; Wadhwa, Sandman, Garite, 2001).

Maternal Prenatal Stressors: Cytokine Balance

Adaptive changes in maternal immunity are vital for the support of pregnancy and the sustenance of the fetus (Elenkov & Chrousos, 1999). Mor (Mor & Cardenas, 2010) identifies a review of immune function during pregnancy, suggesting immune function is not suppressed but rather modulated across pregnancy. Further, the pregnancy is identified immunologically as three distinct phases to shift and accommodate the needs of the developing fetus. While the first phase or early pregnancy is a proinflammatory state to allow for successful implantation, mid-pregnancy is an anti-inflammatory state to allow for rapid fetal growth, and late-pregnancy returns to a proinflammatory state to allow for parturition and delivery of the fetus (Mor & Cardenas, 2010). Alterations in maternal cell mediated immunity permit the growing fetus to be immunologically privileged. Maintenance of a healthy pregnancy requires this shift in maternal cytokine balance toward an anti-inflammatory state (Mor & Cardenas, 2010; Reinhard, 1998). This assertion is supported by observational studies that conclude that women with more

successful pregnancies exhibit higher circulating levels of the anti-inflammatory cytokine IL-10, while women who experience miscarriages have lower levels of IL-10 (Jenkins, 2000; Lim, 1999). Near term in normal pregnancies, a shift to an inflammatory state heralds the onset of labor and delivery of the infant. An increase in proinflammatory cytokines ripens the cervix prior to delivery. Atypical elevations in IL-6, IL-8, and TNF alpha, such as due to infection, are linked to premature birth (Gomez et al., 1995; Zhang, 2000).

It is well-established that psychological stress results in an elevation of proinflammatory cytokines (Witek-Janusek, & Mathews, 2012). Less is known about whether stress-induced overproduction or untimely production of maternal proinflammatory cytokines serves as a possible mechanism whereby maternal stress results in adverse infant outcomes. The work of Ruiz and Coussons-Read, however, demonstrated that women experiencing high levels of stress during pregnancy have increased circulating levels of proinflammatory cytokines late in pregnancy compared to women not experiencing high levels of prenatal stress; (Coussons-Read et al., 2005). Specifically, maternal prenatal stress was associated with higher levels of the proinflammatory cytokines IL-6 and TNF-alpha and with low levels of the anti-inflammatory cytokine IL-10 (Coussons-Read et al., 2005). More recently, Coussons-Read evaluated associations between maternal psychological stress and cytokines during early, mid, and late pregnancy (Coussons-Read et al., 2007). That study showed that during both early and late pregnancy, higher levels of maternal stress was related to elevations in circulating IL-6, while C-reactive protein (CRP) levels were associated with

stress during late pregnancy. Also, elevated prenatal stress was related to lower IL-10 serum levels during early pregnancy. In contrast, no associations were observed with stress and circulating cytokines during the second trimester. The authors conjecture that the lack of associations of stress and cytokines during the second trimester is because this phase of pregnancy reflects a more quiescent time, as the early physical disturbances (i.e., morning sickness, sleep disturbance) that accompany pregnancy have dissipated. In contrast, the third trimester is characterized by stress and anxiety linked to the impending birth. Furthermore, that study also found that elevated levels of maternal stress across pregnancy predicted greater production of IL-1 beta and IL-6 by *ex vivo* LPS-stimulated lymphocytes derived from maternal blood during the third trimester. Thus, these findings provide evidence that elevations in maternal stress during pregnancy can indeed shift cytokine production to a more inflammatory (Th1) state and are consistent with potential mechanisms whereby stress can negatively impact birth outcomes.

Findings from a recent study showed that depressive symptoms were associated with inflammatory biomarkers in pregnant African American women evaluated during the second trimester of pregnancy. That study demonstrated that more depressive symptoms (measured by the CES-D) were associated with greater levels of IL-1beta. Depressive symptoms were also related to IL-6 and IL-10 but these associations were mediated by body mass index (BMI). For leaner women, depressive symptoms were associated with higher IL-6 and IL-10 levels. In contrast, for heavier women depressive symptoms were associated with lower levels of IL-10 (Cassidy-Bushrow, Peters, Johnson, & Templin, 2012). This study did not evaluate whether depression-associated

dysregulation of inflammatory biomarkers affected pregnancy outcomes. It is possible that the disparity in birth outcomes (i.e., lower birth weight, increased preterm delivery, and neonatal neurodevelopmental impairment) observed in African American women may be related to greater depressive symptoms accompanied by excess inflammation.

It is also possible that maternal psychological factors can affect immune development in the infant. There is some evidence that maternal negative mood, such as depression, might alter cytokine balance in the infant (Mattes et al., 2009). Findings show that mild to moderate maternal depression is associated with increased neonatal levels of IL-6 and IL-10, along with increased levels of stimulated cytokine response to bacterial antigens and allergens (Mattes et al., 2009). These results provide suggestive evidence that maternal depression mediates neonatal immune responses, even when depression levels are low to moderate. It is clear that studies investigating maternal stress should include assessments of mood or other emotional states, and that outcome indicators should include maternal as well as infant evaluations.

Effect of Maternal Prenatal Stressors on Adult/Offspring HPA-Immune Activation

Maternal prenatal stress not only results in neonatal adverse effects but also can alter adult stress reactivity. For example, healthy young adults whose mothers experienced severe prenatal stressful events (e.g., death of someone close) were found to exhibit lower cortisol levels prior to being subjected to the Trier Social Stress Test (TSST) and greater increases in cortisol in response to the TSST compared to individuals whose mothers did not experience stressful events during pregnancy. Also the offspring of mothers who experienced more prenatal stressful events produced less cortisol in

response to ACTH but had normal basal diurnal cortisol levels. The results of this study demonstrate that prenatal psychosocial stress exposure in humans predisposes to long-term alterations in the regulation of the HPA axis of adult offspring (Entringer et al., 2009).

Maternal prenatal stress was also shown to influence the immune response of their offspring during adulthood. *Ex vivo* stimulation of peripheral blood mononuclear cells (derived from adult women whose mothers experienced major life stressors during their pregnancy) exhibited a greater IL-2 production relative to interferon gamma as well as increased IL-6 and IL-10 compared to women whose mothers did not experience prenatal stressful events. These findings demonstrate that maternal prenatal stress exposure results in long-lasting effects on immune function of their adult children (Entringer et al., 2008).

Methodological and Design Considerations: Stress Biomarkers

There are many methodological issues to be considered when evaluating whether either cortisol or proinflammatory cytokines mediate the effects of prenatal stress on infant outcomes. For example, many previous studies relied on single assessments during pregnancy. Clearly, there is a need for longitudinal assessment of stress that takes into account the normal changes in the prenatal HPA axis and cytokine balance, as well as changes in maternal psychological state that fluctuate with stage of pregnancy. With respect to cortisol, evidence shows a strong relationship between maternal and fetal cortisol levels; yet the maternal HPA axis fluctuates and changes as a result of maternal response to stress over the course of pregnancy (Talge, 2007). With advancing pregnancy, maternal cortisol steadily increases; while at term gestation, cortisol levels are

increased from the fetus, placenta, and uterus (Benfield, Newton, Tanner, & Heitkemper, 2014). Further, there is a reduction in the ACTH responsiveness to CRH at late-pregnancy (Benfield et al., 2014). Consequently, closer to term there is a reduced maternal capacity to respond to psychosocial stressors or emotional states. It is unknown when the maternal HPA loses responsiveness and how much inter-individual variation there is in HPA responsiveness over pregnancy (O'Donnell, 2009). As noted above, investigators should evaluate diurnal cortisol rhythm to determine its association with indicators of maternal psychosocial stress, anxiety, and/or depression. Also, the placenta "buffers" the fetus from the full effects of maternal cortisol. The placental enzyme, 11β-HSD2, converts much of the maternal cortisol to an inactive metabolite (i.e., cortisone), with only about 10-20% of maternal cortisol crossing over to affect to the fetus (Challis et al., 2001). However, animal models show differential effect of acute versus chronic stress, with chronic stress down-regulating (11β-HSD2) and thus favoring transfer of maternal cortisol to the fetus (Mairesse et al., 2007; Welberg, Thrivikraman, & Plotsky, 2005). Moreover, other evidence suggests that the activity of placental 11β-HSD2 is dependent upon the genetic vulnerability of the mother adding to inter-individual variation (O'Donnell, 2009).

The biological matrix in which cortisol is measured is critical. Currently cortisol can be measured in blood, saliva, urine, amniotic fluid, feces, and, more recently, hair samples. Each of these forms of cortisol assessment has measurement issues. In particular, the procurement of amniotic fluid produces anxiety and may reflect episodic stress and not the specific stress associated with pregnancy or overall life events stress.

Furthermore, the sample source requires different interpretations regarding the timing of the stressor. For example, blood and saliva reflect acute cortisol responses, while cortisol measurement from hair samples reflect cumulative HPA activity over the past few months (D'Anna-Hernandez, Ross, Natvig, & Laudenslager, 2011). Regarding cytokines, studies have relied on plasma or serum levels as well as stimulated production of cytokines. Each of these must be interpreted differently as stimulated cytokines reflect the immune cell's capacity to respond to an artificial (i.e., laboratory) stimulus; whereas circulating cytokines reflect what is available to target cells *in vivo* (albeit, at the time of blood collection).

Given the complex changes in maternal HPA function and maternal-fetal cytokine balance across gestation, the timing of stress and biomarker assessment and corresponding neurobehavioral or physiological outcomes is critical. This is important as different physiological systems develop at specific times and thus there are critical windows of vulnerability to prenatal stress. For example, exposure to prenatal elevated cortisol levels early in gestation was found to be associated with delayed cognitive development over the first year (Davis & Sandman, 2010); whereas, exposure to elevated cortisol levels during late gestation contributed to prematurity (Field, Diego & Hernandez-Reif, 2009; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004). Not only is timing of prenatal stress exposure important to consider, it is also crucial to consider whether the stress exposure was acute or chronic. Chronic stress exposure results in allostatic load or overload and dysregulates HPA function

(McEwen, 2004). In summary, there are many conceptual and methodological issues to consider when evaluating maternal prenatal stress biomarkers.

Other Biological Indicators

Field has proposed that activation of the sympathetic nervous system subsequent to maternal perception of stress during pregnancy might also contribute to poor infant outcomes. Although norepinephrine does not cross the placenta, it can increase uterine artery resistance and decrease placental blood flow; this, in turn, will reduce delivery of oxygen and nutrients to the developing fetus (Field, 2011). Supporting a role for such a possibility is a report which demonstrated that prenatal depression was associated with elevations in both prenatal cortisol and norepinephrine levels, and that furthermore, elevations in norepinephrine were positively associated with low birth weight infants (Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004).

Fetal heart rate variability (HRV) is an index of sympathetic/parasympathetic balance and is also a well-established marker of fetal well-being. HRV indicates vagal tone and serves as a marker of an organism's vulnerability to stress (McEwen, 2003, Porges, 1992 #1524). Studies show that more vulnerable infants, such as those with intrauterine growth retardation, as compared to a normal growing healthy fetus, have less HRV and have more difficulty adapting to the extra-uterine environment (Kikuchi et al., 2006). Maternal psychological factors also influence fetal HRV. In particular, compared to pregnant women with low stress levels, the fetus of pregnant women with high stress levels were shown to exhibit lower HRV. Moreover, the fetus of depressed pregnant women showed higher baseline and delayed heart rate responses to stimulus (Kinsella &

Monk, 2009). Older infants (14 months of age) from prenatal depressed mothers were also shown to exhibit a higher mean heart rate and a lower high frequency component of heart rate variability, indicating lower vagal tone (Dierckx et al., 2009). Others have also shown that infants of mothers with prenatal depression have lower vagal tone, which is associated with reduced attentiveness. These infants exhibit increased right frontal EEG activation, which has been linked to withdrawal behavior; interestingly this was also observed in the depressed mothers, suggesting that the infant mirrored the mother's neurological status (Field, 2011).

Methodological and Design Considerations: Psychosocial Factors

According to the DOHaD or fetal programming model, early exposures to prenatal stress can have long-term consequences that result in harmful outcomes for health across the lifespan. Yet there remain many methodological issues that need to be considered in order to improve the design and advance research in this area. The following addresses issues that pertain to the measurement of maternal psychosocial constructs.

Measurement of Prenatal Psychosocial Stressors

The investigation of stressors during pregnancy is hampered by similar concepts along with measurement issues that are common to stress research in general. A pervasive limitation is the lack of uniformity in the approaches used to measure prenatal stress. Table 1 illustrates a summary of measurement approaches used in previous investigations. A large number of studies evaluating stress during pregnancy utilized instruments that measure perceived stress (such as Cohen's Perceived Stressor Scale—

PSS). These instruments quantify general stress perception by asking respondents how controllable or manageable they perceive events in their life to be. In contrast, other studies evaluate emotions that occur in response to stress, especially maternal prenatal anxiety and depression. Several studies have evaluated stressful life events (i.e., stressors) that have occurred either during pregnancy or within a designated time preceding the pregnancy. This approach often relies on a checklist of life events and respondents are asked to recall whether these events occurred and also the meaning of such events. A few studies took advantage of natural disasters as exemplars of a stressful or traumatic life event. Those studies are strengthened by a clear delineation of the timing of occurrence and duration of the event or stressor with respect to gestation. Pre-conceptual stressors have also been examined to determine their relationship to birth outcomes. Examples include measurement of socioeconomic status and racial discrimination in studies evaluating disparity in birth outcomes (Kramer, Hogue, Dunlop, & Menon, 2011). Few studies have used qualitative approaches or interview methods. These approaches have the advantage of providing a richer understanding of the nature and meaning of stress within the context of the pregnancy.

The variety of approaches used to measure stress attest to differences in how the term "stress" was conceptualized by the investigators. For some studies, stress was conceptualized as a stimulus or event (i.e., stressor). On the other hand, others measure the perception of that event (i.e., perceived stress) or the response to that event (emotional and/or biological). Unfortunately, the lack of conceptual clarity and uniformity among studies adds to the difficulty in interpreting the results, as well as

comparing results across studies. Yet, few studies have acknowledged the complexity associated with measuring stress. Lazarus and Folkman's theory of stress and coping (Lazarus & Folkman, 1984) emphasizes the role of cognitive appraisal in shaping the psychological and physiological response to negative events or stressors. According to this theory, stress occurs only when an event (i.e., a stressor) is perceived as a threat that outstrips an individual's adaptive capacity or resources to cope or deal with that stressor (Lazarus & Folkman, 1984). When perception of a stressor occurs it triggers an emotional response (i.e., anxiety and depression) and also activates the brain, leading to sympathetic nervous system arousal, neuroendocrine activation, and immune system dysregulation. Thus, dependent upon the conceptualization of stress, an investigator may choose to measure the event (i.e., stressor), an individual's perception of the stressor, and/or an individual's response to the stressor (i.e., emotional and/or physiological). This needs to be considered within the context of the research question and the outcomes of interest.

Pregnancy-Specific Stressors

The vast majority of studies investigating prenatal stress have assessed *general life stress*, as opposed to *pregnancy-specific stress*. Failure to measure pregnancy-specific stress can underestimate the source and intensity of stress in pregnant women, as general stress-measurement tools do not include items that reflect the unique experience of pregnancy. This is important because pregnancy-specific stress was shown to be associated with worse poor birth outcomes than was general stress (DiPietro, Ghera, Costigan, & Hawkins, 2004). This emphasizes the importance of measuring the unique

fears and concerns that pregnant women face. Examples of items designed to capture pregnancy-specific stress include: "I am fearful regarding the health of my baby; I am concerned or worried about losing my baby; I am concerned or worried about developing medical problems during my pregnancy" (Sandman et al., 2011a, 2011b).

Positive Emotions during Pregnancy

Pregnancy represents a time of tremendous physiologic and psychological adaptation that occurs in response to the demands of the growing fetus and the anticipation of the infant's birth. Yet, for many women pregnancy is a time of fulfillment and is associated with positive emotions, even in women with low income and few resources (Hawkins, DiPietro, & Costigan, 1999). The assessment of positive emotions during pregnancy has received little attention. Positive emotions are now recognized as distinct constructs and not a polar opposite of negative emotions. In women with high-risk pregnancies, positive emotions were shown to buffer both the emotional distress and adverse birth outcomes associated with these conditions (Lobel, DeVincent, Kaminer, & Meyer, 2000). Moreover, others have identified the *ratio* of pregnancy-associated "daily hassles" to "uplifts" to be the most important measure of pregnancy-related stress (DiPietro, Ghera, Costigan, Hawkins, 2004). Measurement of both positive and negative responses to the experience of pregnancy will provide a more balanced evaluation of stress during pregnancy.

Timing of Stress Exposure

The vast majority of studies have assessed prenatal stress at one time point during gestation. Yet, it is clear that the time of stress exposure is important from both the

maternal as well as the fetal perspective. That is, as pregnancy progresses there are dramatic psychological and physiological adaptive responses that can either increase or attenuate the perception and response to a stressor. Moreover, the maturation of fetal systems follows an orderly developmental pattern with certain organs and tissues exhibiting precise windows of vulnerability to environmental stimuli. Thus, the detrimental outcomes of stress exposure are highly dependent upon the timing of exposure with respect to the period of gestation. Duration of the stressor is also critical, as acute stress exposure may have quite a different effect on birth outcomes than a more enduring or chronic stressor. Studies, which incorporate repeated measures of evaluating the stress response across time, will yield more valid and complete assessments of stressors impacting pregnancy. Also, the timing of stress measurement should be logically linked to the developmental time-frame of the system, organ, or tissue of interest. Finally, the influence of past life events or childhood trauma could have an additive negative insult on the individual.

Postnatal Environment

It is clear that infant/child health outcomes are influenced by interactions between mother and child during the postnatal period. Mothers who experience prenatal stressors are also more likely to have postpartum depression or other mood disorders and, thus, will have poor interactions with their infants and poor parenting styles with their children. As a result, these infants and children are subjected to double jeopardy (i.e., pre- and postnatal stressor exposure) and are most vulnerable. Yet for most studies, the influence of the postnatal environment, especially mother-infant interactions, are not considered or

controlled for. However, some propose a contrasting view. That is, fetuses that experience a harsh prenatal environment, such as that resulting from maternal stress response signals, may undergo adaptive changes that better equip them to respond to a hostile postnatal environment (i.e., poor maternal care). Thus, these infants may, in fact, be more resilient throughout life. Understanding resilience and vulnerability factors is an intriguing area of future research in the field of understanding prenatal stressors and impact on mother-infant health.

Confounding and Moderating Variables

There are a variety of potential confounders that need to be considered when designing a study to determine the effects of prenatal stressors on birth/infant outcomes (Grote et al., 2010; Littleton, Bye, Buck, & Amacker, 2010). Important maternal factors include the following:

- maternal age,
- race,
- education,
- marital status,
- employment,
- SES,
- parity (primparous or multiparous),
- drug use (prescription, over-the-counter, illicit drug use),
- smoking,
- alcohol and caffeine intake,

- obstetric complications,
- co-morbidities (prior depression, and psychological disorders),
- early life stressors
- prenatal care compliance, and
- general health behavior (diet, exercise, weight gain in pregnancy).

Fetal or infant factors to consider in designing research to address birth outcomes include:

- sex
- gestational age,
- birth weight,
- intrauterine growth record,
- birth anomalies,
- genetic-based disease,
- severity of illness,
- length of time in the neonatal intensive care (NICU), and
- complications related to an NICU stay.

As well, there are many potential moderators, which may positively or negatively influence the relationship between maternal perception of and mother-infant health outcomes. Examples of important moderating variables include: life events, marital satisfaction, social support, prior pregnancy experiences, domestic violence, and prenatal care access or compliance with prenatal care recommendations (Grote et al., 2010; Littleton, Bye, Buck, & Amacker, 2010).

In review, experience of prenatal stressors is an important modifiable risk factor. In order to develop and test interventions to reduce prenatal stressors, there is a need to conduct more rigorous observational studies to understand the impact of prenatal stressors on birth outcomes and the psycho-biological mechanism(s) that mediate these adverse effects. As noted by Beydoun and Saftlas (2008), an ideal observational study should have a prospective design, enrollment across pregnancy, with clear assessments of prenatal stress exposure, along with multiple maternal stress assessments, assessment of prenatal and postnatal confounds, and assessments of stress response biomarkers such as CRH, pCRH and cortisol.

Implications and Future Direction

Research examining the impact of maternal prenatal stressors has received considerable attention over many years. Yet despite the wealth of research in this area, additional studies are needed to further advance the state of the science. Examples of future directions for research in this area include the following:

- Studies that link the timing of exposure to stressors during pregnancy with specific maternal-infant outcomes.
- Longitudinal multivariate evaluations of maternal stressors.
- Consideration of gene-environment interactions (single nucleotide polymorphisms for biomarkers, epigenetic markers).
- Expanded incorporation of biomarkers (sympathetic biomarkers, immune biomarkers, epigenetic biomarkers).
- Studies that use mixed methods (i.e., quantitative and qualitative approaches).

- Studies that address what types of stressors are most detrimental.
- Consideration of resilience versus vulnerability factors (i.e., role of marital status, social support, etc.).
- Racial disparity/ health disparity and prenatal stressors.
- Consideration of infant gender (i.e., male infants are more vulnerable).
- Assessment of antecedent variables (i.e., prior life adversity, recent loss/trauma, prior depression or illness).

Prenatal Distress, Epigenetics, and Early Life Programming

The etiology of unfavorable birth outcomes remains unknown and the evidence, as reviewed here, suggests a role for maternal distress and negative mood (e.g., depression). The vast majority of the investigations evaluated prenatal situational stressors and anxiety and show that these factors contribute to birth complications, poor infant health, and increase the risk for long-term adverse health outcomes across the life span. These results are consistent with fetal programming of physiologic systems (e.g., neuroendocrine stress reactivity, immune function), which can contribute to maladaptive responses later in life and risk for adult onset disease.

An area that has received little attention, however, is the relationship between maternal *preconceptional psychosocial stressors* and/or *maternal early life adversity* with birth outcomes. It is possible that maternal preconceptional stressors or adversity, perhaps during early life, might epigenetically program the neuroendocrine and/or immune systems of a woman. As a result, during pregnancy she is potentially incapable of providing a favorable maternal physiologic milieu conducive to optimum birth

outcomes. The capacity of prenatal mood to influence fetal outcomes through epigenetic modification is a new concept that is based on evidence obtained in animal models. Those models show that prenatal and early neonatal stress and/or maltreatment produce long-lasting epigenetic modifications of genes that regulate stress response systems, including the immune system (Mathews & Janusek, 2011). In humans, maternal prenatal depressed mood was reported to be associated with epigenetic modification of the glucocorticoid receptor (GR) in leukocytes obtained from umbilical cord blood. These cord blood leukocytes exhibited increased methylation of DNA at the binding site for transcription factors required to transcribe mRNA that codes for GR. Moreover, the increased DNA methylation was associated with an increase in infant salivary cortisol response. The authors suggest that infants of mothers with prenatal depression are at risk for developing disturbed central regulation of the HPA axis, possibly through an epigenetic process (Oberlander et al., 2008). This is one of few studies in humans that bridge epigenetic modification to GR expression, psychological state (i.e., prenatal depressive mood), and infant cortisol secretion. It is possible that depression dysregulates maternal hormones and results in epigenetic modifications in the neonate. Understanding the role of epigenetics in fetal/neonatal programming that occurs in response to environmental signals (i.e., from the maternal environment) is one of the most intriguing future directions of research in maternal-child health.

Summary

Prenatal psychosocial stressor leads to adverse effects on the newborn that predispose to future mental and physical health problems across the lifespan. To alleviate

these negative outcomes, it is crucial to understand the nature of the stressor that is most devastating, the factors that confer vulnerability versus resilience, and the mechanism(s) explaining how these effects occur. Such understanding can guide approaches for early identification of risk and for the development of interventions to reduce prenatal stressors and subsequently improve the health and well-being of mother, infant and family. The results of such research can offer healthcare providers (particularly nurses) evidence-based practice approaches that ultimately reduce the human and economic costs of the experience of prenatal stressors on mother-infant health. Attaining this goal can exert tremendous benefit, as early life adversity sets up a trajectory for life-long health problems.

CHAPTER THREE

DISCUSSION OF PROPOSED RESEARCH METHODOLOGY

Life Adversity and the Psycho-Neuroendocrine-Immune Profile during Pregnancy

Given the discussion in Chapters One and Two, the overarching objective of this project is to evaluate the influence of a woman's life adversity prior to her pregnancy on her psychological, neuroendocrine, and proinflammatory profile during her pregnancy. In addition, the effect of maternal antenatal life adversity on infant outcomes is evaluated. The central hypothesis of this proposal is that *adverse experiences prior to pregnancy prime stress response systems and lead to increased psychological distress, neuroendocrine activation, and dysregulated proinflammatory cytokine levels*. Such alterations in maternal stress-response systems may contribute to poor infant outcomes.

Specific Aims and Hypotheses

Women were enrolled in this study during the second trimester of their pregnancy to evaluate the specific aims and hypotheses, as listed below:

Aim 1. Examine the relationship between maternal childhood adversity and maternal psycho-neuroendocrine-inflammatory (Kopnisky) profile during pregnancy.

Hypothesis 1. Maternal childhood adversity will be related to maternal psychosocial profile, higher levels of hair cortisol, and higher levels of plasma IL-6 and TNF alpha during pregnancy.

Hypothesis 2. Maternal psychosocial profile during pregnancy will be related to higher levels of maternal hair cortisol plasma IL-6 and TNF-alpha.

Aim 2. Evaluate maternal risk and protective factors as moderators of maternal PNI profile during pregnancy.

Hypothesis 3. Maternal risk (income) and protective (social support) factors will moderate the relationship between maternal childhood adversity and:

a. maternal PNI profile during pregnancy; and
b. neonatal outcomes.

Aim 3. Explore the relationship among maternal childhood adversity, maternal PNI profile during pregnancy, and neonatal outcomes.

Hypothesis 4. Worse neonatal outcomes (lower birthweight and earlier gestational age) will be related to:

a. greater maternal childhood adversity and altered PNI profile during pregnancy; and
b. higher maternal hair cortisol, IL-6 and TNF-alpha levels during pregnancy.

Research Design and Methods

For this study, pregnant women were enrolled and evaluated at three time points (2^{nd} trimester, 3^{rd} trimester and postpartum) to determine the effect of maternal childhood adversity on maternal psychological, neuroendocrine, and inflammatory outcomes. In addition, the effect of maternal prenatal stressors on neonatal outcomes was investigated. This study used a prospective correlational design to evaluate each hypothesis. Sample,

design, measures, and data analysis are described below.

Sample

Pregnant women (18-39 years of age) experiencing uncomplicated singleton pregnancy were recruited from outpatient obstetric health clinics during their first and/or second trimester of pregnancy. Participants were fluent in English, without history of medical or psychiatric disorders requiring hospitalization, major immune-based disease, drug or alcohol abuse, and not taking psychotropic or immune-altering medications.

Recruitment

Pregnant women were recruited from obstetric clinics of a large academic medical center located within the near west suburbs of the major metropolitan area of Chicago (i.e., Loyola University Medical Center and its affiliate, Gottlieb Hospital). Loyola University Medical Center reported 886 live births in 2010; race characteristics were 62% White, 24% Black, 1% Asian, and 12% unknown. Gottlieb Hospital is a community hospital with 742 live births in 2010; race characteristics were 80% White and 18% Black (of these, 20% were Hispanic/Latino and 20% non-Hispanic/Latino).

Overview of Design

Pregnant women were evaluated at three time points during pregnancy. Pregnancy has four trimesters: 1st trimester is 1-12 weeks, 2nd trimester is 13-26 weeks, 3rd trimester is 27-42 weeks gestation, and 4th trimester, postpartum 6 weeks after delivery. Recruitment identified participants early in gestation but data collection did not begin until their 2nd trimester. Initial data collection, Time 1 (T1), took place during the second trimester (16-24 weeks gestation), while Time 2 (T2) occurred during the third trimester

(28-32 weeks gestation), and Time 3 occurred during the 4th trimester (after delivery in postpartum period). See Table 1. tools and data collection time-points.

Table 1. Tools and Data Collection Time-points.

	T1: 16-24 WEEKS GESTATION	T2: 28-32 WEEKS GESTATION	AFTER DELIVERY 1-14 days
BACKGROUND INFORMATION			
Demographic Information	X		
Health History Survey	X	X	
PRIOR LIFE ADVERSITY			
Childhood Trauma Questionnaire	X		
Household Dysfunction	X		
MacArthur Subjective Social Status Scale (MSS)	X		
MODERATING VARIABLES			
Social Provisions Scale (SPA)	X	X	
PSYCHOLOGICAL DATA			
Perceived Stress Scale (PSS)	X	X	
Pregnancy-Related Anxiety (PA)	X	X	
State Trait Anxiety (STAI)	X	X	
Edinburgh Depression Scale (EDS)	X	X	
Depressive Symptoms (CES-D)	X	X	
Mood Disturbance (POMS-65)	X	X	
Pregnancy Experience Scale (PES-Brief)	X	X	
Tilburg Pregnancy Distress Scale (TPDS)	X	X	
The Pittsburg Sleep Quality Index (PSQI)	X	X	
NEUROENDOCRINE DATA			
Hair cortisol (cutting hair)	X	X	
IMMUNE DATA			
IL-6 (blood draw)	X	X	
TNF Alpha (blood draw)	X	X	
NEONATAL OUTCOMES			
Birth Weight (grams)			X
Gestational Age (weeks gestation)			X

Pregnant women will complete self-report instruments to evaluate prior life adversity, which includes the Childhood Trauma Questionnaire, Socio-Economic Status (Trettin, Moses-Kolko, & Wisner, 2006), and the MacArthur Subjective Social Status Scale. It is hypothesized that prior life adversity factors will result in greater psychological distress during pregnancy. The experience of psychological stressors across gestation including perceived stress, pregnancy-related anxiety, depressive symptoms, and mood disturbance was assessed through self-reported questionnaires. HPA activity during pregnancy was evaluated indirectly by measuring cortisol in hair samples. Hair cortisol provides a cumulative index of HPA activity over the preceding three months. Hair cortisol was measured at both second and third trimester (T1 and T2 respectively). Proinflammatory immune activation was determined by measuring plasma IL-6 in blood samples during both the second (T1) and third trimesters (T2) of pregnancy. Neonatal outcomes were assessed to provide exploratory data to evaluate the association between prenatal distress and neonatal development. Birth data (birth weight and gestational age) was obtained from medical records.

Study Variables

Table 2 (see below) lists study variables. Each instrument is included in Appendix E. This list of study variables identifies the independent variables, dependent variables, moderating variables and covariates in this study.

Table 2. Study Variables

Independent Variables	**Dependent Variables**				**Moderating Variables**	**Covariates**
Prior Life Adversity	Psychological	Neuro-Endo-crine	Immune	Neonatal Outcomes		
CTQ	Perceived Stress (PSS)	Hair Cortisol	IL-6 TNF-alpha	Birth weight	Social Support Social Provisions Scale (SPA)	Prenatal Care
Independent Variables	**Dependent Variables**				**Moderating Variables**	**Covariates**
Household Dysfunction	Pregnancy-Related Anxiety (PA) Pregnancy Experience Scale (PES-Brief) Tilburg Pregnancy Distress Scale (TPDS)		Gestational age		Income	Prenatal Compli-cations
SES	Anxiety (STAI)					Health Behaviors
MacArthur Scale	Depression (EDS)					Medication s
	Depression (CES-D)					Demograph ics
	Mood Disturbance (POMS-65)					
	Sleep Disturbance (PSQI)					

CTQ=Childhood Trauma Questionnaire; SES=Socioeconomic status; EDS=Edinburgh Depression Scale; CES-D=Center for Epidemiologic Studies–Depression; STAI=State and Trait Anxiety Inventory; PSQI=Pittsburg Sleep Quality Index

Childhood Adversity

Early life adversity is conceptualized as exposure to adverse experiences prior to 18 years of age, which may originate from the family and/or community. Prior life adversity was measured using the Child Trauma Questionnaire (CTQ). Place of residence is strongly shaped by social position and ethnicity and consequently community characteristics are important contributors to inequities in health. Strong evidence demonstrates that social stressors, like violence, are a clear source of community adversity (Ranjit et al., 2009). Thus, community violence was assessed. Each of the instruments was administered once and is described below.

Child Trauma Questionnaire (CTQ)

The CTQ (Version 3) is a shortened version of the original CTQ, which has improved the reliability among all scales. CTQ is a screening tool that evaluates childhood trauma in five domains: emotional, physical, and sexual abuse, along with emotional and physical neglect. It also includes one scale, made up of three items that evaluate minimization or denial to help identify the under-reporting of traumatic events. In total, it has 28-items and uses a 5-point scale (never true-very often true) to assess frequency of each item. It takes 5-10 minutes to complete and for this study, the time-frame requested is in their first eighteen years of life. CTQ has good internal consistency (range among the five scales, α= 0.69-0.91) and good test-retest reliability. It also has good convergent and discriminate validity when compared with interview-based tools (Bernstein, & Fink, 1997; Bernstein et al., 1994).

Household Dysfunction

This was measured using the scale adapted from the Adverse Child Experience (ACE) study (Felitti et al., 1998), which assesses exposure to substance abuse, mental illness, violent treatment of mother or stepmother, parental separation or divorce, and criminal behavior in the household. Previous research demonstrated a strong graded relationship between exposures to household dysfunction during childhood and multiple risk factors for several leading causes of death in adults (Dube et al., 2009; Felitti et al., 1998). This tool is not a validated tool.

Socio-Economic Status

SES was evaluated for both childhood and current status (Trettin et al., 2006). Childhood SES was assessed by parental occupation, education, childhood place of residence matched with census data, and whether the participant's parents were homeowners. Home ownership correlates with, but is distinct from, traditional measures such as income, and can be more reliably assessed than such measures when assessed retrospectively (Adler, Boyce, Chesney, Folkman, & Smye, 1993). Home ownership has been identified as an independent predictor of improved quality of children's physical and emotional environment, decreased distress, and increased stability (Haurin, 2002). It has been linked to later health, immune function, and inflammation (Chen, 2010; Monroe, 1995; Miller, 2007). Additional SES variables include maternal age, marital status, race, years of education (maternal), and annual household income (ordinal ranking of 1= <10,000 to 10=>90,000).

MacArthur Subjective Social Status Scale (MSS)

This scale uses a ladder metric to determine a person's sense of their place in the social ladder. Respondents view a "social ladder" with 10 rungs, representing where people "stand" in society. The top rung represents those who are best off (most money, most education, best jobs) while the bottom rung represents those who are worst off (least money, least education, worst jobs). Respondents select the rung that best represents their social status (Adler, Epel, Casellazzo, & Ickovics, 2000).

Psychological Stress Measures

Psychological distress measures will use tools to evaluate perceived stress (Perceived Stress Scale), anxiety symptoms (State and Trait Anxiety Index), depressive symptoms (CES-D and EDS), and mood disturbance (Profile of Mood State). Pregnancy specific distress measures were evaluated to determine concurrent validity with more generalized measures of distress including pregnancy-specific anxiety (Pregnancy-Related Anxiety and Pregnancy Experience Scale-Brief), and pregnancy-specific distress (Tilburg Pregnancy Distress Scale).

Perceived Stress Scale (PSS)

Not all stressful events are perceived as stressful. Thus, for the purposes of this study maternal stress perception was measured at T1 and at T2 using the PSS. PSS measures global or overall stress, as opposed to a specific event in the environment, which evokes a stress response. PSS has 10 items, which measure the degree to which experiences are appraised as uncontrollable (S. Cohen & Williamson, 1988). Responses are made using a 5-point Likert scale (0=never, to 4= very often). Scores range from 0-40

with higher scores representing greater stress perception; the time-frame for responses on the PSS represent feelings over the last week. The PSS is a widely used measure of perceived stress (Cohen, 1983, & Mermelstein, 1983; Cohen, 1988 #1275). Cronbach alpha reliability for the total scale ranges from 0.75 to 0.86 (S. Cohen & Williamson, 1988). This scale takes approximately three minutes to complete.

Pregnancy-Related Anxiety (PA)

This is a 10-item questionnaire using a 4-point Likert scale (1= never or almost never, to 4= a lot of the time or very much) to evaluate pregnancy-specific anxiety. The respondent is asked about her feelings regarding health (both self and baby) and about labor and delivery. Scores range from 10-40. Greater scores suggest greater pregnancy-related anxiety symptoms. This tool has good reliability (α=0.78) (Glynn, Schetter, Hobel, & Sandman, 2008; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999).

State and Trait Anxiety Inventory (STAI)

This tool identifies a temporal state of anxiety as compared to a long-standing trait of anxiety. It is a 40-item instrument and the respondent rate items using a 4-point Likert scale (1=not at all, 2=somewhat, 3=moderately so, 4=very much so). Scores range from 20-80 with higher scores representing greater anxiety. It has good reliability and good concurrent validity when compared to other anxiety scales. This scale takes approximately ten minutes to complete; the time-frame for responses on this scale is how they feel generally, without a specific time requested. STAI has been used during pregnancy to evaluate anxiety. However there is a parabolic, U-shaped curve for occurrence of anxiety symptoms across the three trimesters of pregnancy (Teixeira, 2009

Pacheco, & Costa, 2009), with greater maternal anxiety in the first and third trimester. Further there is support for stability of both the state and trait anxiety scores during pregnancy, six weeks after birth, and 24 months after birth (J. A. DiPietro, Costigan, K. A., & Sipsma, H. L., 2008 2008). This support also extends further into development linking pregnancy state and trait anxiety with ADHD in children 8-9 years old (Van den Bergh & Marcoen, 2004).

Profile of Mood States (POM-65)

The POMS consists of 65 items in this scale, which assesses mood state in six domains: tension, anger, confusion, fatigue, vigor, and depression. Respondents use a 4-point Likert scale (0= not at all to 4= extremely) to rate their feelings "right now" or "over the past month" (this study asked specifically their feelings over the past month). Cronbach alpha for internal reliability for the total score ranges from 0.75 to 0.92 (McNair, 1987).

Pregnancy Experience Scale-Brief (PES-Brief)

This tool evaluates both positive and negative stressors across pregnancy. The PES-Brief has ten items identified as pregnancy hassles and ten items as pregnancy uplifts. These items are evaluated on a 4-point Likert scale (0=not at all to 3= a great deal). Time frame for the PES is not specified, but directed as generalized feelings. Cronbach alpha for internal reliability was previously reported to be 0.82 and 0.83 for uplifts and hassles, respectively (DiPietro, Christensen, & Costigan, 2008).

Tilburg Pregnancy Distress Scale (TPDS)

This tool evaluates both pregnancy negative affect and perceived partner involvement. The tool was developed as a pregnancy-specific psychological functioning scale. The TPDS has 16 items with two subscales; negative affect with 11 items and partner involvement with five items. The time-frame for reporting feelings is specified as in the last week. This tool has good internal reliability for the entire scale (0.78) and for each of the subscales (0.80) (Pop, 2011).

Social Provisions Scale (SPA)

This is a 24 item tool evaluates a person's perception of social support that is received from their social relationships. Respondents use a 4-point Likert scale (1= strongly disagree to 4= strongly agree) to indicate either the presence or absence of support. The time-frame for feelings on this tool is not specified as a concrete time but rather a generalized feeling. Cronbach alpha for internal reliability of the total scale was previously reported to be 0.92 (Cultrona, 1987).

Edinburgh Depression Scale (EDS)

This is a 10-item instrument used to evaluate both prenatal and postnatal depression symptoms. Respondents rank each item on a 4-point Likert scale (0=never or rarely, to 3= often or usually). The time-frame for responses on the EDS is for feelings over the last week. The scores range from 0-16 and scores $\geq$13 indicate depression risk, warranting further clinical intervention. Negatively worded items are reverse scored (items 3, 5, 6, 7, 8, 9, 10) (Cox, Holden, & Sagovsky, 1987; Murray & Cox, 1990).

Center for Epidemiologic Studies Depression Scale (CES-D)

This tool is widely used to evaluate self-reported generalized depressive symptoms in a general population. It is a 20-item instrument that asks respondents how they felt or behaved over the last week, using a 4-point Likert scale (0=rarely to none of the time, less than 1 day, to 3=most or all of the time, 5-7 days). Scores range from 0-60 with greater scores suggesting greater depressive symptoms (with scores $\geq$16 suggesting clinical depression). It has good reliability (α= 0.85-0.90) in healthy and patient subjects. Also, the scale demonstrates good test-retest reliability with high internal consistency and very good concurrent validity by both clinical and self-reported criteria. This scale takes approximately three minutes to complete. (Radloff, 1977).

The Pittsburg Sleep Quality Index (PSQI)

This includes 19 self-rated items as a sleep quality measurement tool. The tool also includes partner-rated items that are not included in the scoring of the tool. PSQI evaluates sleep over the last week. In a sample of pregnant women, Cronbach alpha for internal consistency was reported to range from 0.72 to 0.78 in pregnant women which has been evaluated during the second and third trimesters (0.72 to 0.78 respectively) (Skouteris, Wertheim, Germano, Paxton, & Milgrom, 2009).

Maternal Biological Outcomes

Hair Cortisol Rationale

Cortisol becomes incorporated in the hair shaft and recently hair cortisol has been shown to be a reliable measure of HPA activity in humans. Hair cortisol provides an integrated measure of cortisol over a longer time frame and thus is useful for study

designs that require a long-term evaluation of cortisol (D'Anna-Hernandez, 2011; Natvig, & Laudenslager, 2011).

Hair Cortisol Measurement

For the measurement of hair cortisol, hair was collected from the posterior vertex region of the head during the second and third trimester of pregnancy. Thinning shears (scissors) were used to cut a 1-cm^2 patch of hair, as close to the scalp as possible and as recommended by the Society of Hair Testing (approximately 50 hair strands) (Stalder & Kirschbaum, 2012; Testing, 1997). After cutting, the proximal end of the hair sample was secured with tape onto aluminum foil and wrapped for shipment to the laboratory of Dr. Mark Laudenslager, at the University of Colorado Denver, Anschutz Medical Campus. Hair was analyzed for cortisol in Dr. Laudenslager's laboratory, where he has developed a reliable measurement technique for evaluating hair cortisol and is a leading expert in this procedure.

The methods for processing hair samples were consistent with an earlier study process and briefly described below (Hoffman, Karban, Benitez, Goodteacher, & Laudenslager, 2014). Hair was cut, collected, and secured with light adhesive tape onto aluminum foil, then labeled with study participant identification number and date in a consistent pattern with the cut portion of the hair sample for analysis, above the taped portion of hair. Hair was sent in batches and processed collectively with both time-points for each respective participant, at the same time. Hair was collected stored and processed in the lab of Dr. Laudenslager. Hair was washed three times in isopropanol alcohol and dried for four days. After this process was complete, hair was weighed, then ground and

processed as described by Hoffman and colleagues (Hoffman et al., 2014). Then, after drying, extracts were reconstituted with 133µl of buffer and commercial high-sensitivity EIA kits used to determine cortisol levels (Salimetrics, LLC, State College, PA, USA). To determine a control sample, an inter-assay coefficient of variation (CV) was used from a previous ground hair sample, and processed on the same plate with new samples. Intra-assay coefficient of variation (CV) for the control sample was 4.1%, while the intra-assay CV was 11%.

Cytokine IL-6 Rationale

Of the three classic proinflammatory cytokines, IL-6 is the key inflammatory response mediator (Hirano, Akira, Taga, & Kishimoto, 1990; Kishimoto, 2005; Ohzato et al., 1992). IL-6 is chosen as representative of an exemplary proinflammatory cytokine, as it is more dependably detected and evaluated than the other classic proinflammatory cytokines (TNF alpha and IL-1 beta) (Fernandez-Botran, Miller, Burns, & Newton, 2010). Also, adults exposed to childhood maltreatment exhibit an exaggerated IL-6 response (Carpenter et al., 2010) when subjected to acute laboratory stressors and exhibit elevations in circulating IL-6 when under chronic stress (Kiecolt-Glaser et al., 2010). Coussons-Read and colleagues evaluated associations between maternal psychosocial stress and cytokines during early, mid and late pregnancy (Coussons-Read et al., 2007). That study showed that during both early and late pregnancy, a greater exposure to maternal stressors was related to elevations in circulating IL-6.

Cytokine IL-6 Measurement

Blood (20 ml) was obtained in the early afternoon (1-3 PM) in a uniform manner (Nagabhushan, 2001; Witek-Janusek, Albuquerque, Chroniak, Chroniak, Durazo-Arvizu, & Mathews, 2008; Witek-Janusek, Gabram, & Mathews, 2007). Plasma IL-6, was determined as described previously (Witek-Janusek, Albuquerque, Chroniak, Chroniak, Durazo-Arvizu, & Mathews, 2008; Witek-Janusek, Gabram, & Mathews, 2007), using commercial ELISA kits (R&D Systems, Minneapolis, MS). Intra- and inter-assay coefficients of variation were previously reported to be 9.2% and 2.8%, respectively.

Cytokine TNF Alpha Rationale

Of the 3 classic proinflammatory cytokines, TNF alpha is another key inflammatory response mediator (Sedger & McDermott, 2014) and is frequently evaluated during pregnancy. It has both anti-viral and anti-bacterial effects. TNF alpha is associated with bacteria in amniotic fluid during pregnancy. When comparing premature delivery to term delivery, elevations in cytokine TNF alpha was predictive of earlier gestational age (Coussons-Read, Lobel, Carey, Kreither, D'Anna, Argys, Ross, Brandt, Cole, 2012).

Cytokine TNF Alpha Measurement

Blood (20 ml) was obtained in the early afternoon (1-3 PM) in a uniform manner (Nagabhushan, 2001; Witek-Janusek, Albuquerque, Chroniak, Chroniak, Durazo-Arvizu, & Mathews, 2008; Witek-Janusek, Gabram, & Mathews, 2007). Plasma TNF-Alpha, was determined as described previously (Witek-Janusek, Albuquerque, Chroniak, Chroniak,

Durazo-Arvizu, & Mathews, 2008; Witek-Janusek, Gabram, & Mathews, 2007), using ELISA commercial ELISA kits (R&D Systems, Minneapolis, MS).

Neonatal Outcomes

Neonatal outcomes will include infant birth weight and gestational age. Birth data was obtained from the medical record after delivery. The birth weight was recorded in grams, while the head circumference and length was recorded in centimeters.

Gestational Age

This was an estimate obtained from the medical record based on the mother's last menstrual period and/or by ultrasound measurement, if available.

Covariates

Several potential covariates were included in the model based on previous research indicating they may be related to study outcome variables while others were conceptually identified including week prenatal care started. Maternal covariates that were controlled for in the statistical analysis included the following: prenatal care, pregnancy complications, pre-pregnancy BMI (Christian, Franco, Glaser, & Iams, 2009), and demographics (age, education, income (Ronald, Pennell, and Whitehouse, 2011), etc.). Inclusion of covariates were determined from previous research investigating stressors during pregnancy and maternal infant outcomes. The covariates included the following: maternal age, parity, BMI pre-pregnancy (Bolten et al., 2011), income, race (bivariate), and education.

Statistical Analysis

The independent variables to be evaluated for this study include measures of childhood adversity, as well as maternal psychosocial stressors. Dependent variables will include hair cortisol, plasma IL-6, plasma TNF alpha, and neonatal outcomes (birthweight and gestational age). Each variable was evaluated for distribution and residuals for normality, linearity, homoscedasticity, homogeneity, and multicollinearity. Analysis was performed using IBM SPSS Statistics Standard GradPack 23 for Mac.

A series of regression models were used to evaluate study hypotheses. For Aims 1 and 2, regression models will evaluate the contribution of childhood adversity factors on each of the psychological, neuroendocrine, TNF-alpha, and IL-6 variables for each time point (i.e., second and third trimesters of pregnancy). Each adversity factor including income, and position in community and society using rungs on a ladder, using the MacArthur Subjective Status Scale was evaluated as a predictor of outcomes. Also a single factor, as a composite score to represent childhood adversity using Principal Component Analysis (PCA), was unable to be created because variables were uncorrelated. The childhood adversity composite score was composed of measures of childhood trauma, income, and social status. Moderators (i.e., risk and protective factors) for each model were evaluated to determine their contribution and/or interaction with childhood adversity factors (Aim 2). Covariates (health behaviors and demographics) were initially evaluated (Stage 1) to determine associations with outcome variables. Only those covariates found to have significant associations ($p<0.05$) were retained in the final models.

Each distress factor was evaluated as a predictor of outcomes. Also a single factor was created as a composite score to represent stress, using PCA. The "Distress Composite Score" was composed of measures of generalized depression, generalized anxiety, perceived stress, mood dysfunction, and sleep disturbance. A composite score was established given the ability to compress into a single composite score, to establish a single construct.

For exploratory Aim 3, correlations was determined between measures of neonatal outcome and (a) maternal childhood adversity factors, (b) maternal prenatal distress, (c) maternal hair cortisol, (d) maternal TNF-alpha, and (e) maternal IL-6. These correlations were determined at each time point (T1 and T2). Exploratory regression models were also evaluated to determine which of the maternal variables best-predicted neonatal outcomes.

Power Analysis

There are seven predictors in the proposed model: prior life adversity (independent variable), income and social support (moderating variables), the interaction between prior life adversity and each of the moderating variables, and health risk factors and age (covariates). Using a G* power 3.1 analysis to determine the sample size, using a medium effect size (0.2), α error probability 0.05, power 0.80, with seven predictors in the model, an estimate of 80 pregnant women would be needed to have sufficient power to run a multiple linear regression. A smaller sample would be needed to accomplish the bivariate correlations.

Protection of Human Subjects

Participants signed an informed consent prior to enrollment into the study. The informed consent for Loyola University Medical Center and Gottleib Hospital was submitted to the IRB at Loyola University. The informed consent included a description of the purpose of the research project, procedures involved including two blood draws for evaluation of immune function, cutting of two samples of hair to evaluate hair cortisol as a physiologic measurement of HPA activity over the past three months, and risks and benefits. Participants were told that participation was voluntary and that they could withdraw at any time by notifying the investigator. Further, clarification of the distinction between research and clinical care for the participant and their newborn was provided. Potential participants were given the opportunity to ask questions.

While there are minimal risks to this research study, there is some risk related to the blood draws, including pain, discomfort, or possible bruising from the procedure. A trained phlebotomist or Registered Nurse to ensure consistent procedures was done on all blood draw procedures. The blood sampling was necessary to evaluate immune function during pregnancy and compare these findings to psychological data and hair cortisol. The investigator obtained all hair samples, as instructed by Dr. Mark Laudenslager. Hair cortisol provided information regarding HPA of participant's activation over the last three months. Hair was cut as close to the scalp as possible, in the posterior vertex region, as described earlier (see "Hair Cortisol Measurement"). Thinning shears were used to collect approximately 50 strands of hair to minimize the visual impact. Participants were compensated $50.00 at study completion for providing the two blood collection

procedures. They were still compensated regardless of whether or not they provided all questionnaires or hair sample, but provided a blood sample.

CHAPTER FOUR

RESULTS

Enrollment and Data Collection

This study was approved by Loyola University Medical Center, Institutional Review Board. Data were collected from November 2012 to November 2014. Ninety-five healthy low-risk pregnant women were enrolled during their first or second trimester of pregnancy. Women were recruited from Loyola University Medical Center, Women's Health Clinic, as well as from associated satellite clinics of Loyola University. Of the 95 women enrolled, fourteen women withdrew from the study for the following reasons: Five did not respond to follow-up phone calls, one electively terminated pregnancy for congenital anomalies, one thought questionnaires were too personal, one withdrew because it required too much effort for her to provide blood and to complete study questionnaires, two were too busy, and three women were electively withdrawn because of medical reasons (prior hemorrhage with last pregnancy, thrombocytopenia with current pregnancy, and Hashimoto's thyroiditis). Lastly, the investigator withdrew one woman after she fainted in clinic during the study blood draw. [Note: This was reported to her physician and the Institutional Review Board as an adverse event.]

Women were assessed at Time 1 (between 16-24 weeks gestation, second trimester) and at Time 2 (between 28-32 weeks gestation, third trimester). Of the 95

women enrolled, only a portion completed all measures for each time point. For Time 1, a total of 64 women provided data for all biologic variables and all questionnaires.For Time 2, only 44 women provided data for these measures. For hair cortisol assessment, 66 and 52 women agreed to hair collection at Time 1 and Time 2, respectively.

Data for depression, anxiety (STAI trait), maternal childhood adversity before 18 years of age (CTQ), maternal hardship before 18 years of age (Blackmore et al., 2006), maternal medical complications, infant complications, APGAR scores, birthweight and gestational age were also collected after delivery.

Demographic Description of the Sample

A description of the sample demographics is illustrated in Table 3. The mean age of those enrolled (N=95) was 27.7 years (SD= 5.6, range 18-39 years). The ethnic and racial characteristics of the enrolled sample were as follows: 27.7% identified as Hispanic/Latino and 28.3% White, 23.4% African American, 2.1% Asian, 3.2% more than one race, and 5.3% other race or did not specify. Women were primarily married (43%), single (20%), and divorced or separated (1%). The highest educational degree earned was an Associates or Bachelor's degree (41%), followed by a high school diploma or GED (27%), with 22% reporting some graduate training (22%). Nearly 22% of the sample reported a household income less than $9,999; 11% reported an income between $10,000 to $29,000; another 11% reported an income between $30,000 to $49,000; 16% reported an income between $50,000 to $69,000; and about 40% reported a household income equal to or greater than $70,000. About half of the women had home ownership (or someone in household owned the home), while the remainder lived in a rented home.

Using Federal poverty guidelines, based on income and family size, it was determined that 23% of the sample were living in poverty. Most women (64%) worked full-time during their pregnancy, 15% worked part-time, 8% were unemployed/laid off or looking for work, and 2% were students. In addition, 13% percent of the women replied that they were "homemakers".

Table 3. Demographics

Race/Ethnicity	Frequency	Percent
White	36	38.3
African American	22	23.4
Other	5	5.3
Asian	2	2.1
More than one race	3	3.2
Hispanic/Latino	26	27.7
Age at Consent	Frequency	Percent
18-20	12	14.1
21-30	43	50.6
31-39	30	35.3
Marital Status	Frequency	Percent
Single	20	31.3
Married	43	67.2
Divorced/Separated	1	1.6
Employment Status	Frequency	Percent
Full-time	39	62.9
Part-time	9	14.5
Homemaker	8	12.9
Unemployed	5	8.1
Student	1	1.6
Household Income	Frequency	Percent
Less than $9,999	14	22.2
$10,000-$19,000	3	4.8
$20,000-$29,000	4	6.3

Table 3. Demographics (cont.)

$30,000-$39,000	5	7.9
$40,000-$49,000	2	3.2
$50,000-$59,000	3	4.8
$60,000-$69,000	7	11.1
$70,000-higher	25	39.7
Education Level	Frequency	Percent
High School Incomplete	7	11.1
High School Diploma or GED	17	27.0
Associates Degree	6	9.5
Bachelor's Degree	18	28.6
Master's Degree	9	14.3
Professional (MD, JD, DDS, etc)	3	4.8
Other	4	6.4

Pregnancy and Health Descriptive Data

Sample characteristics of the women enrolled in this study are illustrated in Table 4. In this sample of women, 49% reported this pregnancy as a planned pregnancy. This pregnancy was confirmed at six weeks or earlier in 87% of the sample. Most women were multiparas (86%). Among multiparas women, 20.9% had one or more miscarriages, as compared to national average in the PRAMS nationwide database of 14.9 % (Robbins et al., 2014). Nearly all women (92%) had regular health care before pregnancy. Most women reported both good to excellent physical and mental health prior to pregnancy (93% and 96%, respectively). Both tobacco and alcohol use pose considerable adverse health consequences to mother-infant health. In the sample, 5% percent reported smoking, and 6% used alcohol during this pregnancy. As a comparison, national averages for smoking are 18%, while alcohol use is reported as 54% in women prior to pregnancy (Robbins et al., 2014).

About 80% of the sample expressed happy feelings about their pregnancy, while 19% of women reported feeling unhappy or having ambivalent feelings about their pregnancy. Those feeling unhappy during mid-pregnancy is particularly concerning given that this time of pregnancy is a relatively quiescent time of pregnancy (Sandman, & Davis, E. P., 2012).

Co-morbidities prior to pregnancy were also assessed. None of the women reported hypertension, diabetes, or eating disorder, while 8% reported anemia, 5% thyroid problems, 8% asthma, 5% depression, and 14% anxiety disorder. These rates are lower than the national averages for pre-pregnancy diabetes at 2.1% and hypertension at 3.0% (Robbins et al., 2014). Some women experienced complications by the end of their pregnancy (40%). This was most often pregnancy-induced hypertension (11%), followed by gestational diabetes (9%). Women with these risk factors either before pregnancy or during pregnancy pose additional health concerns to mother-infant health. These pregnancy complications are listed in Table 5.

Fifty percent of women in this study reported their pregnancy as unplanned, in comparison to national average (43%) reported by the PRAMS study in 2009. In the U.S., approximately half of all pregnancies are unintended (Finer & Zolna, 2011). Women most likely to have an unintended pregnancy are low-income women, and this is inversely related to education level. Further, there continues to be ethnic and racial disparities; low-income Hispanic women have the highest rate of unplanned pregnancy while African American women in both low-income and high-income had the highest rate of unplanned pregnancy (Finer & Zolna, 2011).

Table 4. Sample Characteristics

	Frequency	Percent
Primaparas	9	14.3
Miscarriages 1 or 2	13	20.9
WIC before this pregnancy	18	28.6
Regular health care before this pregnancy	58	92.1
Fertility treatment for this pregnancy	3	4.8
Daily Prenatal Vitamins before pregnancy	18	28.6
Daily Prenatal vitamins (in the last month) during pregnancy	49	77.8
Using birth control when got pregnant	10	16.1
Unplanned pregnancy	32	50.8
Rate Physical Health Before Pregnancy	Frequency	Percent
Excellent	19	30.2
Good	40	63.5
Fair	18	6.3
Rate Mental Health Before Pregnancy	Frequency	Percent
Excellent	32	51.6
Good	27	43.5
Fair	3	4.8
Week of gestation when pregnancy confirmed	Frequency	Percent
6 or less weeks	53	86.9
7 or greater	8	13.1

Table 4. Sample Characteristics (cont.)

When pregnancy confirmed, how did you feel?	Frequency	Percent
Very happy	38	61.3
Somewhat happy	12	19.4
Somewhat unhappy	5	8.1
Very unhappy	3	4.8
Unsure how I felt	4	6.5
Describe pregnancy overall	Frequency	Percent
One of the happiest times of my life	14	24.1
Happy time without many problems	32	55.2
Moderately hard time	8	13.8
Very hard time	4	6.9

Table 5. Pregnancy Complications

	Frequency	Percent
Pregnancy Complications (any)	39	39.8
Gestational Diabetes	9	9.2
Hypertension/ Pregnancy Induced Hypertension (PIH)	11	11.2
Anemia	1	1.0
Infection-chorio-amnionitis	1	1.0

Prenatal vitamins were taken less frequently before conceiving (51% took prenatal vitamins), while a majority (78%) took them daily in the second trimester. In comparison, prenatal or before conception vitamin use is lower than the national rates (29.7%) (Robbins et al., 2014). Regarding health care insurance prior to this pregnancy, 10% reported no health insurance coverage, 66% reported private health insurance (Blue Cross and Blue Shield, HMO), and 24% had public health insurance. In comparison to

national averages of 75% reporting health insurance coverage prior to pregnancy, this study has 15 % higher rates of insurance coverage than the national average (Robbins et al., 2014). Additionally, 29% reported receiving WIC prior to this pregnancy. Most women conceived naturally without fertility treatment.

Most women delivered vaginally, with 43% undergoing a cesarean delivery. As a comparison, the national average for cesarean delivery is 33%. All women delivered live infants, and 40% delivered a female infant. The mean infant birthweight was 3229.4 grams (SD= 547.3, range 950-4180 grams), and mean gestational age was 38.4 (SD= 1.99, range 27-41 completed weeks). See Table 6 for descriptive information on infant birthweight and gestational age. Delivery information is listed in Table 7 and Table 10. Only 9% of women delivered a premature infant (i.e., less than 37 weeks gestation). Also, 9% of the women delivered a low birthweight infant (< 2500 grams), while 1% delivered a very low birthweight infant (<1500 grams), and 1% delivered an extremely low birthweight infant (<1,000 grams). As expected, most of the women delivering prematurely also delivered a low birthweight infant. As a comparison, birth data from the 2013 National Vital Statistics Report report premature delivery accounting for 11.4%, low birthweight delivery accounting for 8.0%, and very low birthweight delivery accounting for 1.4%, of all births. Additionally, for comparison, national averages for low birthweight rates are 8.0% for all women. The low birthweight rates continue to be greatest in African American women at 13.1% followed by Hispanic women at 7.1% and White women at 7.0%. Illinois state average for premature birth was 12.2% in 2013, which is slightly higher than the national average. In light of these national and state data,

as a comparison, the current study sample had lower averages for premature infant delivery and for low birthweight delivery (Martin, Hamilton, Curtin, & Mathews, 2015).

The Apgar score is a simple standardized evaluation tool used to evaluate all newborns in the hospital setting. APGAR is an acronym for Appearance, Pulse, Grimace, Activity and Respiration, which are the tools five categories. See Table 9 for a visual description and scoring system of the tool. This quick evaluation is done at one, five, and ten minutes of age. Infants are rated on a scale of 0-2 for each of the five categories. It is used to evaluate the infant's transition to the extra-uterine environment, but is not predictive of long-term outcomes. APGAR scores are impacted by prematurity, medications during delivery, resuscitation, cardio-respiratory compromise, and neurologic issues (Practice, 2015). Infants with scores of 0-3 are severely depressed, 4-6 moderately depressed, and 7-10 in normal condition (Newborn, 2006). See Table 8 for APGAR scores in this sample, and Table 9 for a diagram of the Apgar scoring system. At one minute of age, 3.9% of the infants were severely depressed, 3.9% were moderately depressed, while at five minutes none of the infants were severely depressed and 1.3% were moderately depressed. At ten minutes of age all of the infants were in the normal range.

Table 6. Infant Descriptive Statistics: Birthweight and Gestational Age

	N	Min	Max	Mean	SD
Birthweight	81	950.00	4180	3229.42	547.33
Gestational Age	80	27.00	41.00	38.43	1.99

Table 7. Infant Descriptive Statistics: Delivery

	N	Percent
Term Delivery 37-42 weeks	73	91
Premature Delivery <37 weeks	7	9
Average Weight Delivery (AGA) ≥2500 grams-4200 grams	74	91.4
Low Birthweight Delivery (LBW) <2500 grams-1500 grams	5	6.2
Very Low Birthweight Delivery (VLBW) <1500 grams-1000 grams	1	1.2
Extremely Low Birthweight Delivery (ELBW) <1000grams	1	1.2

AGA: 2500-4200gm (5lb 8oz - 9lb 4oz), LBW: 2500 grams (5lb 8oz), VLBW: <1500 grams, (3lb 5oz). ELBW: <1000gms, (2lb 3oz)

Table 8. Infant Descriptive Statistics: APGAR Scores

	APGAR 1 Minute		APGAR 5 Minute		APGAR 10 Minute	
Score	Frequency	Percent	Frequency	Percent	Frequency	Percent
Range 1-3	3	3.9	0	0	0	0
Range 4-6	3	3.9	1	1.3	0	0
Range 7-10	72	92.3	77	98.7	62	100

Note: Scores 0-3: Severely depressed; Scores 4-6: Moderately depressed; Scores 7-10: Normal condition

Table 9. Apgar Scoring System

	0 Points	1 Point	2 Points	1 Min. Total	5 Min. Total	10 Min. Total
Activity	Absent	Arms and legs flexed	Active movement			
Pulse	Absent	Below 100 BPM	Above 100 BPM			
Grimace, reflex irritability	Flaccid	Some flexion of extremities	Active motion (cough, sneeze, pull away			
Appearance (skin color)	Blue, pale	Body pink extremities blue	Body and extremities pink			
Respiration	Absent	Slow, irregular	Vigorous cry			
Totals						

BPM= beats per minute.
Note: scores 0-3: severely depressed; scores 4-6: moderately depressed; scores 7-10: normal condition.

Table 10. Delivery Method

Delivery Type	Frequency	Percent
Normal Vaginal Delivery	46	57.5
Caesarean Delivery	34	42.5

Table 11. Anticipated Feeding Choice at Mid-Pregnancy

Feeding Method	Frequency	Percent
Breastfeeding	36	46.8
Formula	23	29.9
Combination	18	23.4

Breastfeeding is the optimal nutrition for infants; The World Health Organization (Organization, 2001; Phillips et al., 2000) and the American Academy of Pediatrics

(AAP) recommends exclusive breastfeeding for the first six months of life for optimal growth, nutrition, and development (Section on, 2012 2001). Despite these recommendations, women are influenced by personal, physical, social, environmental (Cunningham, 2009), and medical reasons (Section on, 2012). Rates of breastfeeding remain low in women with lower education (without college education), women living in poverty, African American women, and younger women (Center for Disease Control and Prevention, 2013). Healthy People 2020 include specific aims to increase breastfeeding rates in women at initiation, and to sustain exclusive breastfeeding through the first six months, and beyond through the first 12 months of age (U.S. Department of Health and Human Services, 2011). In this study, 47% of the women evaluated during the second trimester anticipated breastfeeding, 30% formula feeding, and 23% a combination of both breast and bottle feeding (see Table 11). Additionally, 44% mothers reported being breastfeed as an infant, while 49% reported not being breastfeed as an infant. In 71% of the sample, they reported that their friends breastfed their own infants, while 24% said their friends did not breastfeed. These personal and social factors influence the rates of breastfeeding initiation and duration for mothers in this study.

Weight and height were used to calculate BMI. Mean BMI for pre-pregnancy weight was 28.4kg (N=60, SD=6.5, range 16.8-46.2 kg), and mean BMI in second trimester of pregnancy was 26.5kg (N=62, SD= 6.5, range 17.7-47.5). Weights for participants came from self-report. About 3% of women had pre-pregnancy weights categorized as underweight, 50.8% normal weight, 18.6% overweight, and 27.6% obese. At mid-pregnancy, those who were underweight were 1.6%, normal weight was 34.4%,

overweight was 27.9%, and obese was 36.1%. In comparison, National and local Illinois rates of obesity (BMI 30 or greater) before pregnancy, through the 2009 PRAMS self-report, were 22.1% and 20.2%, respectively (Robbins et al., 2014; Farr, et al., 2014).

Descriptive Statistics: Psychosocial and Behavioral Measures

Women completed self-report instruments that assessed general and pregnancy specific measures of depression (CES-D, EDS), anxiety (STAI, PAS), fatigue/distress (TPDS), pregnancy experience (PES), and sleep quality (PSQI). Women also completed instruments measuring mood (POMS-65), perceived stress (PSS), social support (SPA), and maternal childhood trauma (CTQ) (prior to 18 years of age). Additionally, demographic information was obtained and a health history was completed.

Key Variables

Each key variable is discussed in the following sections. Tables 23 and 24 identify the descriptive statistics of the psychological variables for T1 and T2 including; sample size, range of scores, mean, standard deviation, and percent above standard cut score for each measurement tool. Additionally, internal consistency of the tools is presented. The key variables are: perceived stress, depression, anxiety, mood disorder, social support, sleep, and maternal childhood trauma (trauma before 18 years of age). Additionally, nurse/scientist-derived tools to investigate pregnancy specific measures were evaluated for concurrent validity to evaluate stressors experienced during pregnancy. Each of these tools are used less commonly in the literature, but may be useful to administer in the clinical setting. These include the following: the Tilburg Pregnancy Distress Scale (TPDS) to evaluate pregnancy distress, Pregnancy Anxiety

Scale (PAS) to evaluate pregnancy specific anxiety, and the Pregnancy Experience Scale (PES) to evaluate pregnancy experience.

Perceived stress. The Perceived Stress Scale (PSS) was used to measure generalized perception of stress in the last month of the second and third trimester of pregnancy. Scores for T1 ranged from 5-36 (N=64, m=16.1, SD= 7.3), with 63% above the population mean of healthy women, score of greater or equal to 13 (listed as a cut score in the graph); while scores for T2 ranged from 1-36 (N= 44, m=12.9, SD= 6.9), with 52% above population mean. A cut score of 13 was determined based on normative sample mean (Sheldon Cohen & Janicki-Deverts, 2012). Internal consistency for PSS in this sample was strong (α= 0.89). Descriptive statistics are listed in Table 12.

Table 12. Descriptive Statistics: Perceived Stress Scale (PSS)

	N	Min	Max	Mean	SD	% Cut score[1]
Perceived Stress T1	64	5.00	36.00	16.08	7.33	63
Perceived Stress T2	44	1.00	31.00	12.89	6.92	52

1= Percentage of sample above cut score (based on population mean of healthy adult women) for each measure
Perceived Stress (PSS) cut score: $\geq$13

Depression. Screening for depression during pregnancy and the postpartum period is currently recommended by the American College of Obstetrics and Gynecologists (ACOG) (Practice, 2015), while the American Academy of Pediatrics (AAP) recommends depressive risk screening in the postpartum period (Earls & Committee on Psychosocial Aspects of Child Family Health, 2010). ACOG recommends all women be screened at least once during their pregnancy. Only the American Psychological Association (APA) recommends universal screening of all women for

postpartum depression, but this screening has not been accepted as a standard of care. [Note: There is an Act to provide funding in 2015 for universal screening of all women through the Melanie Blocker Stokes MOTHERS Act, but it has not been funded and accepted as a standard of care by Congress to this date. While there is no mandate requiring universal screening in all women, some states are moving toward this initiative, such as the state of New Jersey.]

While both the EDS and CES-D are depressive risk tools, the EDS is a pregnancy specific measure of depressive risk (the CES-D is a generalized measure of depressive risk). Both are used in research studies; however, the CES-D is used much more frequently. The EDS is currently being used on all pregnant women at several times across pregnancy and into postpartum.

The Center for Epidemiological Studies Depression Scale (CES-D) was used to measure generalized depressive symptoms in the second and third trimester of pregnancy. Scores for T1 ranged from 0-53 (N=64, m=12.9, SD= 11.9) with 28% above the cut score ($\geq$16); while scores for T2 ranged from 4-29 (N= 44, m=7.8, SD= 4.88), with 7% above the cut score (see Table 13 for descriptive information on CES-D). Internal consistency for CES-D in this sample was strong (α= 0.94).

Table 13. Descriptive Statistics: Center for Epidemiological Studies Depression Scale (CES-D)

	N	Min	Max	Mean	SD	% Cut score[1]
Depression CES-D T1	64	.00	53.00	12.91	11.93	28
Depression CES-D T2	44	4.00	29.00	7.75	4.88	7

1= Percentage of sample above cut score for each measure
Depression cut score (CES-D) cut score: $\geq$16

The Edinburgh Depressive Scale (EDS) was used to measure pregnancy specific depressive symptoms in the second and third trimesters and after delivery (Cox, Chapman, Murray, & Jones, 1996; Cox, Holden, & Sagovsky, 1987). Original authors suggest cut scores could range from 9-13 (Cox, Holden, & Sagovsky, 1987). More current literature suggests clinical depressive risk cut score of 13 or greater, while the American Academy of Pediatrics suggests a cut score of ten or greater for probable depressive risk screening (Earls & Committee on Psychosocial Aspects of Child Family Health, 2010). For consistency in this analysis, a cut score of 13 or greater was used. Scores for T1 ranged from 0-24 (N=64, m=6.7, SD= 6) with 10% above the cut score score at or above 13; while scores for T2 ranged from 0-16 (N= 44, m=4.5, SD= 4.0) with 7% above the cut score; see Table 14 for descriptive information on EDS. Internal consistency for EDS in this sample was strong (α= 0.86). Use of the EDS and EPDS has been validated for use across pregnancy and into the postpartum. EDS is used to represent Edinburgh Depression Scale before delivery while the EPDS is used to represent Edinburgh Depression Scale after delivery (postpartum). The EDS and EPDS are the exact same assessment tool with the same questions, but represent different time frames of administration; either during pregnancy, or postpartum, respectively. Table 14 below identifies both the EDS and EPDS for comparison purposes. The EDS at Time 1 had greater mean scores than any other time-point. Further, EDS mean at Time 2 measured at 24-32 weeks identified via study questionnaire, and EDS mean at approximately 28 weeks gestation during routine medical appointment and obtained from the medical record was consistent. Lowest mean values for EPDS were in the postpartum

period either soon after delivery or at the six-week check per medical record report. In a large meta-analysis there were differences in cut scores across multiple studies based on determining the best trade-off based on sensitivity and specificity; it is believed that cultural differences could contribute to higher or lower cut scores (Kozinszky & Dudas, 2015). Findings from a validation study measuring depressive symptoms across pregnancy (based on 845 White women) suggest a cut score of 10 to provide adequate sensitivity and specificity, and positive predictive value (Bergink et al., 2011). In this research, a predetermined cut score was based on cut scores determined a priori, by initial tool development. Additionally, it was protocol for any identified person scoring 1, 2, or 3 on question 10, which addresses suicidal thoughts of harming themselves or their baby, to be referred for additional screening. In this study, three participants (5%) listed some thoughts of harming themselves in the second trimester of screening, necessitating immediate primary care physician, nurse practitioner notification: One had a history of depression, one had pregnancy complications (gestational diabetes), and one had no documented preexisting conditions.

Table 14. Descriptive Statistics: Edinburgh Depression Scale (EDS)

	N	Min	Max	Mean	SD	% Cut score[1]
Edinburgh Depression Scale T1	64	0	24.00	6.746	6.00	25/11
Edinburgh Depression Scale T2	44	0.00	16.00	4.50	4.01	14/7

1= cut scores ≥10/≥13; Edinburgh Depression (EDS) cut score: ≥13 (clinical depressive risk). (AAP recommends EDS ≥10 should get referral however in this paper, cut scores of ≥ 13 is used)

Table 15. Descriptive Statistics: Edinburgh Depression Scale (EDS) and Edinburgh Postpartum Depression Scale (EPDS)

	N	Min	Max	Mean	SD
EDS T1	63	0.00	24.00	6.75	4.86
EDS T2	44	0.00	16.00	4.50	4.01
EDS 28	69	0.00	18.00	4.72	4.02
EPDS PP	78	0.00	12.00	2.88	2.99
EPDS 6 Weeks PP	57	0.00	16.00	2.56	3.21

Note: EDS is used to represent Edinburgh Depression Scale before delivery
EPDS is used to represent Edinburgh Depression Scale after delivery (postpartum).
The EDS and EPDS are the exact same assessment tool with the same questions, but represent different time frames of administration; either not postpartum, or postpartum, respectively.

Anxiety. The State Anxiety Inventory (STAI) was used to measure generalized anxiety symptoms in the second and third trimesters of pregnancy. Scores for T1 ranged from 20-70 (N=64, m=36.5, SD= 13.1), while scores for T2 ranged from 20-78 (N= 44, m=34.4, SD= 12.2). Internal consistency for STAI in this sample was strong (α= 0.96). Normative data is based on a sample of non-pregnant women (N= 210, M= 36.17, SD= 10.96, α= .92) (Speilberger, 1983). STAI range of scores in this study is consistent with normative ranges of non-pregnant women at Time 1 and slightly lower than normative ranges at T2 or T3. Women scoring above the cut score for STAI of greater than thirty-six at mid-pregnancy (41%), late-pregnancy (24%), and remaining elevated at post-pregnancy (22%), are displayed in Table 16 below.

Table 16. Descriptive Statistics: State Anxiety Scale (STAI)

	N	Min	Max	Mean	SD	>36[a]
STAI T1	64	20	70.00	36.47	13.05	41%
STAI T2	42	20	78.00	34.40	12.20	24%
STAI T3	18	20	69.00	30.78	13.34	22%

a= mean score for STAI measure, normative sample in women 19-39 years old was 36.17 (SD=10.96).

The Pregnancy Anxiety Scale (PAS) was used to measure pregnancy specific anxiety symptoms in the second and third trimester of pregnancy. Scores for T1 ranged from 11-34 (N=63, m=18.1, SD= 4.9); while scores for T2 ranged from 10-27 (N= 43, m=16.7, SD= 4.3); see Table 17 below for descriptive statistics on PAS. Internal consistency for PAS in this sample was strong (α= 0.78). Elevated pregnancy-specific anxiety using the PAS is associated with a negative long-term impact on the incidence of anxiety in 6-9 year-old children. Further, PAS and not STAI-State anxiety scale in mid-gestation (25 weeks as compared to 20 or 30 weeks gestation) was the single greatest predictor of childhood anxiety. A study by Davis and Sandman (2012) showed a 10% elevated risk for pre-adolescent anxiety for every 1-point increase on PAS, consistent with an earlier large study using the PAS (mean scores at 20, 25, 30 weeks gestation M= 18.8, SD 4.6) (Buss, Poggi Davis, Pruessner, Head, and Sandman, 2012).

The PAS in mid-pregnancy is correlated with perceived stress (PSS), depression (CES-D and EDS), anxiety (STAI state), and low social support (SPA) and poor sleep (PSQI global). See Tables 18 and 19 below for correlations on the PAS at Time 1 and Time 2 with key distress variables. This tool was only used to establish concurrent validity of the tool with other more generalized measures of stressors across pregnancy

therefore, these correlations were not corrected for a Type 1 error using a Bonferroni correction. This supports fair concurrent validity of this tool to evaluate pregnancy specific anxiety during mid-pregnancy. PAS in late-pregnancy was approaching significance for the same tools mentioned above with mid-pregnancy.

Table 17. Descriptive Statistics: Pregnancy Anxiety Scale (PAS)

	N	Min	Max	Mean	SD
PAS T1	63	11	34.00	18.06	4.87
PAS T2	43	10	27.00	16.70	4.33

Table 18. Correlations: Key Stress Variables with PAS Time 1

		PSST1	EDST1	CESDT1	POMST1	STAIT1	SPAT1	PSQI GlobalT1
PAS T1	r	.289*	.286*	.287*	.162	.338**	-.397**	.04

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 19. Correlations: Key Distress Variables with PAS Time 2

		PSST2	EDST2	CESDT2	POMST2	STAIT2	SPAT2	PSQI GlobalT2
PAS T2	r	.266	.289	.322*	.307	.303	-.287	.243

** Correlation is significant at the 0.01 level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed).

Mood disturbance. Profile of Mood Scale (POMS-65) was used to measure generalized mood symptoms in the second and third trimesters of pregnancy. Scores for total mood disturbance scores for T1 ranged from 11.0-114.0 (N=53, m=20.3, SD= 25.3); while scores for T2 ranged from -11 -105 (N= 35, m=17.7, SD= 28.3). Internal consistency for POMS-65 in this sample was strong (α= 0.94). Range of scores for POMS-65 subscales tension-anxiety, depression-dejection, anger-hostility, vigor-activity,

fatigue-inertia, confusion-bewilderment (9 items, range 0-36, 15 items, range 0-60, 12 items, range 0-48, 8 items, range 0-32, 7 items, range 0-28 respectively); normal range of scores for POMS-65, Total Mood Disturbance is 0-200 (Curran, 1995; McNair, Lorr, & Droppleman, 1992). For women scoring above cut scores based on normative mean, see Table 20 for descriptive statistics, while Tables 21 and 22 show the subscales for Time 1 and Time 2. Approximately 11-13% of the sample scored above the cut scores for tension, depression, anger, confusion subscales, while 21% scored above the cut scores for fatigue, and 61% scored above the cut scores for vigor. It is important to note that the sample varies among the subscales because not all women responded to every question on the tool; therefore, there is a variation in the sample size for the subscales.

Table 20. Descriptive Statistics: POMS-65

	N	Min	Max	Mean	SD
Total Mood Disturbance T1	53	-11.00	114.00	20.28	25.25
Total Mood Disturbance T2	35	-11.00	105.00	17.66	28.28

Table 21. Descriptive Statistics: POMS-65 Subscales T1

	N	Min	Max	Mean	SD	>Cut Score[3]
Mood Disturbance Tension-Anxiety	55	2.00	27.00	8.63	5.53	12.2%
Mood Disturbance Depression-Dejection	60	.00	41.00	7.43	9.59	12.2%
Mood Disturbance Anger-Hostility	58	.00	33.00	7.21	7.11	9.8%
Mood Disturbance Vigor-Activity	59	3.00	27.00	15.00	4.99	64.9%
Mood Disturbance Fatigue-Inertia	56	1.00	24.00	8.46	4.89	17.5%
Mood Disturbance Confusion-Bewilderment	57	.00	19.00	6.33	3.79	10.3%

a= mean score for POMS-65, subscale cut scores: Tension-Anxiety M= 16, SD= 8.9, α= .92, Depression-Dejection M= 20, SD= 14.5, α= .95, Anger-Hostility M= 16, SD= 10.7, α= .92, Vigor-Activity M= 12, SD=7.5, α= .93, Fatigue-Inertia, Confusion-Bewilderment M= 12, SD= 6.4 α= .86.

Table 22. Descriptive Statistics: POMS-65 Subscales T2

	N	Min	Max	Mean	SD	> Cut Score[a]
Mood Disturbance Tension-Anxiety	41	.00	25.00	8.32	5.49	10.9%
Mood Disturbance Depression-Dejection	41	.00	38.00	5.73	8.73	13.3%
Mood Disturbance Anger-Hostility	41	.00	33.00	6.46	7.13	12.1%
Mood Disturbance Vigor-Activity	37	2.00	25.00	16.00	5.59	61.0%
Mood Disturbance Fatigue-Inertia	40	1.00	19.00	7.38	4.43	21.4%
Mood Disturbance Confusion-Bewilderment	39	1.00	17.00	6.13	3.67	12.3%

a= mean score for POMS-65, subscale cut scores: Tension-Anxiety M= 16, SD= 8.9, α= .92, Depression-Dejection M= 20, SD= 14.5, α= .95, Anger-Hostility M= 16, SD= 10.7, α= .92, Vigor-Activity M= 12, SD=7.5, α= .93, Fatigue-Inertia, Confusion-Bewilderment M= 12, SD= 6.4 α= .86.

Sleep. Sleep quality during the second and third trimester of pregnancy was assessed using the Pittsburgh Sleep Quality Index (PSQI). Global Sleep for T1 ranged from 0-18 (N=64, m= 6.84, SD= 3.51, with 59.4% above the cut score; while scores for T2 ranged from 0-16 (N=45, m= 6.89, SD=3.32), with 55.6% above the cut score. Descriptive statistics for the PSQI are listed below in Table 23. Internal consistency for PSQI in this sample was strong (α= .79). A global PSQI cut score of > 5 represents poor sleep quality. Women in this sample scoring above the cut scores were (n=38) 59.4% and (N=25) 55.6% for T1 and T2, respectively. In comparison, in a similar study investigating sleep in women during late pregnancy, 69% of the sample scored above the cut score (Okun, Hanusa, Hall, & Wisner, 2009).

Table 23. Descriptive Statistics: Pittsburgh Sleep Quality Index Global Sleep (PSQI)

	N	Min	Max	Mean	SD	% Cut Score[1]
Global Sleep T1	64	1	18	6.84	3.51	59.4 (n=38)
Global Sleep T2	45	2	16	6.89	3.32	55.6 (n=25)

1= cut off scores > 5 Global Sleep (poor sleep quality)

Social support. Social Provisions Scale (SPA) was used to measure social support in the second and third trimester of pregnancy. Social support for T1 ranged from 51-96 (N=64, m=84.5, SD= 10.3); while T2 ranged from 52-95 (N=44, m=87.1, SD= 9.4). Descriptive statistics are listed in Table 24 for total scores while Tables 25 and 26 list descriptive information on the subscales for Time 1 and Time 2, respectively. Internal consistency for SPA in this sample was strong (α= 0.92).

Table 24. Descriptive Statistics: Social Provisions Scale (SPA)

	N	Min	Max	Mean	SD	% Cut Score[1]
Social Support T1	64	51.00	96.00	84.47	10.34	81.3%
Social Support T2	44	52.00	95.00	87.05	9.42	86.4%

a= mean score for Social Provisions Scale (SPA) measure, normative sample based on N=1036 adults, was 78.85 (SD=10.37).

Table 25. Descriptive Statistics: Social Provisions Scale (SPA) Subscale T1

	N	Min	Max	Mean	SD	% Cut Score[1]
Social Support Total T1	64	51.0	96.0	84.47	10.34	81.3%
Attach Support T1	64	8.0	16.0	14.45	2.21	82.8%
Social Integration Support T1	64	6.0	16.0	13.50	2.20	73.4%
Reassurance of Worth Support T1	64	8.0	26.0	14.00	2.61	76.6%
Reliable Alliance Support T1	64	6.0	16.0	14.75	2.13	76.6%
Guidance Support T1	64	6.0	16.0	14.44	2.47	82.8%
Opportunity for Nurturance Support T1	64	5.0	16.0	13.33	2.44	67.2%

1= Percentage of sample above cut score for each measure
Normative range Social Provisions Scale Total (N= 1036, M= 78.85, SD= 10.37, α= .93), cut scores >79, Attach >13, Social >13, Reassure >13, Reliable >14, Guidance >13, Opportunity >13 (Cutrona & Russell, 1987).

Table 26. Descriptive Statistics: Social Provisions Scale (SPA) Subscales Time 2

	N	Min	Max	Mean	SD	% Cut Score[1]
Social Support Total T2	44	52.0	95.0	87.05	9.42	86.4%
Attach Support T2	44	8.0	16.0	14.86	1.88	86.4%
Social Integration Support T2	44	8.0	16.0	14.00	2.00	77.3%
Reassurance of Worth Support T2	44	5.0	16.0	14.23	2.23	81.8%
Reliable Alliance Support T2	44	7.0	16.0	14.95	1.88	79.5%
Guidance Support T2	44	9.0	16.0	15.00	1.76	88.6%
Opportunity for Nurturance Support T2	44	8.0	16.0	13.93	2.14	67.2%

1= Percentage of sample above cut score for each measure
Normative range Social Provisions Scale Total (N= 1036, M= 78.85, SD= 10.37, α= .93), cut scores >79, Attach >13, Social >13, Reassure >13, Reliable >14, Guidance >13, Opportunity >13 (Cutrona & Russell, 1987).

Table 27. Descriptive Statistics: Psychological Variables Time 1

	N	Min	Max	Mean	SD	% Cut Score[1]
Perceived Stress (PSS) Time 1	64	5.00	36.00	16.08	7.33	63
General Depression CES-D) T1	64	.00	53.00	12.91	11.93	28
Edinburgh Depression (EDS) T1	64	0	24.00	6.746	6.00	25/11
Social Support (SPA) T1	64	51.00	96.00	84.47	10.34	81
Total Mood (POMS-65) T1	53	-11.00	114.00	20.28	25.25	Na
General Anxiety (STAI) T1	64	20.00	70.00	36.47	13.05	41
Sleep Quality (PSQI Global) T1	64	1.00	18.00	6.84	3.51	59

[1]= Percentage of sample above cut score for each measure
Perceived Stress (PSS) cut score: ≥13
Depression cut score (CES-D) cut score: ≥16
Edinburgh Depression (EDS) cut score: ≥13 (clinical depressive risk)
(AAP recommends EDS ≥10 should get referral)
Global Sleep (PSQI) cut score: >5
PSS based on normative mean.
STAI based on normative mean.
SPA based on normative mean.
na = not applicable; no established cut score for the total mood disturbance.

Table 28. Descriptive Statistics: Psychological Variables Time 2

	N	Min	Max	Mean	SD	% Cut Score[1]
Perceived Stress (PSS) T2	44	1.00	31.00	12.89	6.92	52
General Depression (CES-D) T2	44	4.00	29.00	7.75	4.88	7
Edinburgh Depression (EDS) T2	44	0.00	16.00	4.50	4.01	14/7
Edinburgh Depression (EDS) 28 weeks from EMR	69	0.00	18.00	4.72	4.02	4
Social Support (SPA) T2	44	52.00	95.00	87.05	9.42	86
Total Mood (POMS-65) T2	35	-11.00	105.00	17.66	28.28	na
General Anxiety (STAI) T2	42	20.00	78.00	34.40	12.20	24
Sleep Global (PSQI Global) T2	45	3.00	16.00	7.11	3.34	62

1= Percentage of sample above cut score for each measure
Perceived Stress (PSS) cut score: $\geq$13
Depression cut score (CES-D) cut score: $\geq$16
Edinburgh Depression (EDS) cut score: $\geq$13 (clinical depressive risk)
(AAP recommends EDS $\geq$10 should get referral)
Global Sleep (PSQI) cut score: >5
PSS based on normative mean.
STAI based on normative mean.
SPA based on normative mean.
na = not applicable; no established cut score for the total mood disturbance.

Pregnancy Distress (Negative Affect and Partner Involvement)

The Tilburg Pregnancy Distress Scale (TPDS) is a pregnancy distress scale (Pop, 2011). It also has subscales to evaluate pregnancy affect and perceived partner involvement in the second and third trimester of pregnancy. Pregnancy distress (TPDS total scale, with 16 items) T1 ranged from 1-39 (N=62, M=12.89, SD= 8.16) and T2 ranged from 0-35 (N=44, M=11.59, SD= 8.57); descriptive information on the total scales and subscales are listed below in Table 29. The subscales for the TPDS are Negative Affect and Partner Involvement. TPDS Negative Affect for T1 ranged from 1-31 (N=12, M=7.98, SD= 8.86), and TPDS Partner Involvement for T1 ranged from 1-14

(N=62, M=3.19, SD= 3.60); while TPDS Negative Affect for T2 ranged from 1-24 (N=10, m=6.78, SD= 9.38) and TPDS partner involvement for T2 ranged from 1-13 (N=44, m=2.86, SD= 3.27). Internal consistency for TPDS total scale and each subscale (Negative Affect and Partner Involvement) was strong (α= 0.87, 0.86, .086, respectively). As a comparison, this data is consistent with normative values of the TPDS total scale with sixteen items (N= 304, Range 0-37, M= 10.67, SD= 5.81, α= .78). Normative values on the subscales Negative Affect (NA) with five items and Partner Involvement (PI) with eleven items is consistent with study values (N= 304, Range 0-14, M= 4.20, SD= 2.90, α= .80, N= 304, Range 0-23, M= 6.46, SD= 4.70, α= .81, respectively) (Pop, 2011).

The TPDS in mid-pregnancy and late-pregnancy is highly correlated with perceived stress (PSS), depression (CES-D and EDS), anxiety (STAI state), mood disturbance, and low social support (SPA); further, it is also correlated with poor sleep (PSQI global) See Tables 29 and 30 below (note, these correlations were not corrected for a Type 1 error using a Bonferroni correction). This supports concurrent validity of TPDS to evaluate pregnancy distress during both mid-pregnancy and late-pregnancy.

Table 29. Descriptive Statistics: Tilburg Pregnancy Distress Scale (TPDS)

	N	Min	Max	Mean	SD
Pregnancy Distress T1	62	1	37	12.89	8.16
Pregnancy Distress T2	44	0	35	11.59	8.57
TPDS Subscales:					
TPDS Negative Affect T1	61	0	29.00	9.66	6.22
TPDS Partner Involvement T1	62	0	14.00	3.19	3.60

Table 29. Descriptive Statistics: Tilburg Pregnancy Distress Scale (TPDS) (cont.)

TPDS Negative Affect T2	10	0	24.00	6.78	9.38
TPDS Partner Involvement T2	44	0	13.00	2.86	3.27

Table 30. Correlations: Key Distress Variables with TPDS Time 1

		TPDST1	PSST1	EDST1	CESD T1	POMS T1	STAIT 1	SPAT1	PSQI GlobalT1
TPDS T1	r	1	.582**	.624**	.593**	.443**	.719**	-.618**	.262*

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Table 31. Correlations: Key Distress Variables with TPDS Time 2

		TPDST2	PSST2	EDST2	CESD T2	POMS T2	STAIT 2	SPAT2	PSQI GlobalT2
TPDS T2	r	1	.428**	.580**	.490**	.442**	.472**	-502**	.293*

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Pregnancy Experience

The Pregnancy Experience Scale (PES) was used to evaluate positive and negative stressors across pregnancy. Further, positive and negative stressors are conceptualized by the original authors as pregnancy uplifts and hassles in the second and third trimester of pregnancy (DiPietro, Christensen, & Costigan, 2008). This is illustrated in Table 32. Internal consistency for PES in this sample was strong (α= 0.79).

The Pregnancy Experience Scale (PES) subscales measure pregnancy affective valance frequency and pregnancy affective valance intensity. Pregnancy affective valance frequency at mid-pregnancy is highly correlated with perceived stress (PSS),

depression (CES-D and EDS), anxiety (STAI state), mood disturbance (POMS), poor sleep (PSQI global) and low social support (SPA); while at late pregnancy it is correlated with STAI (state) and approaching significance with low social support. See Tables 33 and 34 below for correlation tables; note, these correlations were not corrected for a Type 1 error using a Bonferroni correction, given that this tool was used to establish concurrent validity with generalized measures of stressors across pregnancy. Pregnancy affective valance intensity at mid-pregnancy and late-pregnancy is highly correlated with perceived stress (PSS), depression (CES-D and EDS), anxiety (STAI state), mood disturbance (POMS), and poor sleep (PSQI global), and low social support (SPA). This supports concurrent validity of the PES to evaluate pregnancy experience during both mid-pregnancy and late-pregnancy.

Table 32. Descriptive Statistics: Pregnancy Experience Scale (PES)

	N	Min	Max	Mean	SD
Pregnancy Uplifts Frequency T1	63	5.00	10.00	9.08	1.29
Pregnancy Hassles Frequency T1	63	1.00	10.00	6.59	2.56
Pregnancy Uplifts Intensity T1	63	1.00	3.00	2.28	0.47
Pregnancy Hassles Intensity T1	63	1.00	2.78	1.49	0.50
Pregnancy Uplifts Frequency T2	44	6.00	10.00	9.43	0.97
Pregnancy Hassles Frequency T2	44	2.00	10.00	6.89	2.35
Pregnancy Uplifts Intensity T2	44	1.20	3.00	2.41	0.45
Pregnancy Hassles Intensity T2	44	1.00	2.63	1.47	0.39

Table 33. Correlations: Key Distress Variables with PES Time 1

	PES Freq T1	PES Inten T1	PSS T1	EDS T1	CESD T1	POMS T1	STAI T1	SPA T1	PSQI Global T1
PES Freq T1	1	.571**	.457**	.359**	.329**	.420**	.361**	-.198	.346**
PES Inten T1		1	.583**	.574**	.607**	.451**	.571**	-.459**	.449**

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 34. Correlations: Key Distress Variables with PES Time 2

	PES Freq T2	PES Inten T2	PSS T2	EDS T2	CESD T2	POMS T2	STAI T2	SPA T2	PSQI Global T2
PES Freq T2	1	.557**	.217	.242	.219	.248	.359*	-.291	.250
PES Inten T2		1	.520**	.590**	.673**	.610**	.649**	-.579**	.463**

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Childhood Trauma

The Childhood Trauma Questionnaire (CTQ) was used to measure maternal childhood adversity before 18 years of age in the pregnant mother. This was assessed in women after delivery. The maternal childhood adversity (CTQ) cut score determines frequency and intensity of abuse and neglect. These range in four categories (none, low, moderate, severe) for each of the five subscales on the CTQ. Subscales on the CTQ

include emotional neglect and abuse, physical neglect and abuse, and sexual abuse. The CTQ total score ranged from 25-89 (N=53, M=33.4, SD= 12.7). Table 35 identifies descriptive statistics for the CTQ. Internal consistency for CTQ in this sample was strong (α= 0.93). The study results on the CTQ subscales included, emotional neglect with scores ranging from 5-24 (N=53, M=7.8, SD= 4.3), emotional abuse with scores ranging from 5-25 (N=53, M=7.3, SD= 4.0), physical neglect with scores ranging from 5-15 (N=53, M=6.36, SD= 2.9), physical abuse with scores ranging from 5-23 (N=53, M=6.3, SD= 2.8), and sexual abuse with scores ranging from 5-15 (N=53, M=5.7, SD= 2.0).

As a comparison, the normative values for the total scores on the CTQ in a community sample of women between 25-44 (N=511)= 32.48 (11.58) (Scher, Stein, Asmundson, McCreary, & Forde, 2001) Additionally, subscales on the CTQ, in a large HMO sample of women shows good internal consistency (N=1225, α= 0.83.4) (Bernstein, & Fink, 1997) which is consistent with the findings in this study and are presented below. The observations in this study are likely consistent with the large sample size in the HMO study, based on its large size and the greater likelihood of having cases of less severe childhood trauma. Further, for comparison, normative values include emotional neglect and abuse (M=10.5, SD= 5.0, α= 0.92 and M=9.2, SD= 4.8, α= 0.85, respectively) physical neglect and abuse (M=6.6, SD= 2.7, α= 0.63, and M= 6.9, SD= 3.4, α= 0.92, respectively) and sexual abuse (M=6.8, SD= 4.2, α= 0.93) (Bernstein, & Fink, 1997). The use of these cut scores for the subscales are based on normative values and provides consistency when comparing values across different studies. While the CTQ

total does not have an established cut score yet as identified above, a cut score was established based on a community sample mean of 32.48 (Scher et al., 2001). Pregnant women scoring above cut score for CTQ total is 34% (n=18). For this study, Table 36 below lists the percentage and number of participants that fall within the cut scores for each of the four levels of maltreatment on the CTQ. The four levels of maltreatment are none (minimal), low, moderate, and severe. Women reporting moderate to severe childhood trauma from emotional neglect were 9.5% (n=5), emotional abuse 5.7% (n=3), physical neglect 13.2% (n=7), physical abuse 5.7% (n=3), and sexual abuse 11.3% (n=6).

Table 35. Descriptive Statistics: Childhood Adversity

	N	Min	Max	Mean	SD	% Cut Score[1]
Maternal Childhood Trauma	53	25.00	89.00	33.38	12.67	34.0 (n=18)
CTQ Emotional Neglect	53	5.00	24.00	7.81	4.28	9.5 n=5
CTQ Emotional Abuse	53	5.00	25.00	7.25	3.95	5.7 n=3
CTQ Physical Neglect	53	5.00	15.00	6.36	2.91	13.2 n=7
CTQ Physical Abuse	53	5.00	23.00	6.25	2.81	5.7 n=3
CTQ Sexual Abuse	53	5.00	15.00	5.72	2.01	11.3 n=6

1= Percentage of sample above Cut score for each measure total scale mean 32.48 (Scher et al., 2001) and subscales emotional neglect 10, emotional abuse 9, physical neglect 8, physical abuse, 8, sexual abuse 6 (Bernstein, & Fink, 1997; Bernstein et al., 1994).

Table 36. Descriptive Statistics: Maternal Childhood Adversity Cut Scores

	None[1]		Low[1]		Moderate[1]		Severe[1]	
	N	%	N	%	N	%	N	%
Emotional Neglect Cut Score	41	77.4%	7	13.2%	3	5.7%	2	3.8%
Emotional Abuse Cut Score	43	81.1%	7	13.2%	0	0.0%	3	5.7%
Physical Neglect Cut Score	44	83.0%	2	3.8%	1	1.9%	6	11.3 %
Physical Abuse Cut Score	45	84.9%	5	9.4%	2	3.8%	1	1.9%
Sexual Abuse Cut Score	45	84.9%	2	3.8%	4	7.5%	2	3.8%

1= Cut scores for each subscale and each of the four levels of maltreatment.
Emotional Neglect: None (or minimal) 5-9, Low 10-14, Moderate 15-17, Severe $\geq$18
Emotional Abuse: None (or minimal) 5-8, Low 9-12, Moderate 13-15, Severe $\geq$16
Physical Neglect: None (or minimal) 5-7, Low 8-9, Moderate 9-12, Severe $\geq$13
Physical Abuse: None (or minimal) 5-7, Low 8-9, Moderate 10-12, Severe $\geq$13
Sexual Abuse: None (or minimal) 5, Low 6-7, Moderate 8-12, Severe $\geq$13
(Bernstein, & Fink, 1997; Bernstein et al., 1994).

MacArthur Subjective Status Scale

This scale identifies the self-perceived standing of the pregnant mother on an illustrated social ladder. The internal consistency in this scale is good (α= 0.74) based on the two items—rungs on the ladder. Rungs on the ladder are ranked as the following: 1 is the lowest rung on the ladder, the lowest subjective placement in community (or U.S.A.); whereas 10 is the highest rung on the ladder, the highest subjective placement in the community (or USA). Table 37, listed below, illustrates responses on the MacArthur Subjective Status Scale. Study data regarding responses to rungs on a ladder in a community (N=60, Range 2-10, M= 6.02, SD= 2.00), and rungs on a ladder in the USA (N=59, range 1-10, M= 5.46, SD= 2.24). This is consistent with normative data from a

large sample (N=1294, range 1-10, M=5.85, SD=1.78, age 18-60+, 55% women and 76% White). Further, the study participants ranked where they placed in a community—steps 1-3, 4-7, 8-10 (13.3%, 63.3%, 23.3%, respectively)—while the normative sample ranked steps 1-3, 4-7, 8-10 (10%, 74%, and17%, respectively). Both the normative data and the study sample are both slightly above the midpoint for the mean scores (Operario, Adler, & Williams, 2004).

The study sample participants were well-educated, with a majority (60.4%) having some college education. Women reported their educational level as less than high school diploma 9.5%, high school diploma or GED 27%, Associates or Bachelor's degree 38.1%, and Master's or Doctorate degree 22.3%. In comparison, the educational level is much higher than normative ranges from a large, national, multi-ethnic sample where the participants reported less than high school 9%; high school diploma 53%; or some college, college degree, or graduate education 39% (Operario et al., 2004). Many of the women worked full-time 63.5%, followed by raising children or keeping house 15.9%, working part-Time 14.8%, unemployed/laid off 4.8%, and looking for work 1.6%. The greatest percentage of women (67.1%) earned less than $50,000 annually. Household size, based on how many were in the household including self, was three or more for 63% of the sample. Additionally, 72.6% had one child while 27.4% had two to five children in the household. Further, 82% had two to three adults living in the home. In this sample, 50% had home ownership, while 45% rented their home. When participants were asked about the availability of emergency funds, 75% reported that they had enough money to last 12 months or less at the same standard of living. When subtracting all debt from

credit cards, loans, etc., most women (35.5%) had less than $5,000 on reserve in accounts. However, a third of the sample (29%) did not answer this specific question.

Table 37. Descriptive Statistics: MacArthur Subjective Status Scale

Rungs on a Ladder: Place Yourself in Community	N=60	Frequency	Percent
Rungs 1-3		8	13.3
Rungs 4-7		38	63.3
Rungs 8-10		14	23.3
Rung 1 Lowest Placement, Rung 10 Highest Placement			
Rungs on a Ladder: Place Yourself in USA	N=59		
Rungs 1-3		13	22.0
Rungs 4-7		34	57.7
Rungs 8-10		12	20.4
Rung 1 Lowest Placement, Rung 10 Highest Placement			
Highest grade (years in school)	N=63		
8-12 grade		18	28.7
13-16		24	36.2
17-20		19	28.6
Highest Degree Earned	N=63		
Incomplete High School		6	9.5
High School Diploma/GED		17	27
Associates Degree/Bachelor's Degree		24	38.1
Master's Degree/Doctorate/Professional MD/JD/DDS, etc.		14	22.3
Other		2	3.2
Daily Activities and Responsibilities	N=63		
Working Full-time		40.0	63.5
Working Part-time		14.3	14.3
Unemployed or Laid Off		3.0	4.8
Looking for Work		1.0	1.6
Keeping House or Raising Children		10.0	15.9
How Much Do You Earn	N=61	Frequency	Percent
<49,999		42	67.1
50,000-74,999		10	16.4
75,000-99,999		2	3.3
100,000->		2	3.3
Unwilling to answer/don't know		6	9.8
How Many in Household Including Self	N=62		
1-2 people		38	37.1
3-4		29	46.8
5-7		10	16.2

Table 37. Descriptive Statistics: MacArthur Subjective Status Scale (Cont.)			
How Many Are Children	N=62		
0-1		45	72.6
2-3		15	24.2
4-5		2	3.2
How Many are Adults	N=62		
0-1		5	8.1
2-3		51	82.3
4-5		6	9.7
Of the Adults, How Many Bring Income to Home	N=61		
0-1		15	24.6
2-3		44	72.2
4-5		2	3.2
Is your Home:	N-60		
Owned or Being Bought by You		30	50.0
Rented		27	45.0
Occupied Without Payment		1	1.7
Other		2	3.3
Income in Past 12 months	N=61		
<49,999		22	36.1
50,000-74,999		11	18
75,000-99,999		8	13.1
100,000->		12	19.7
Unwilling to Answer/Don't Know		8	13.1
If Lost All Income, How long Could You Live With Standard of Living	N=60		
Less than 1 Month		12	20
1-2 Months		12	20
3-6 Months		15	25
7-12 Months		6	10
More than 1 Year		15	25
If You Needed Money Quickly, How Much Do You Have With All Savings/Checking Accounts	N=62		
<$500		10	16.1
500-4,999		12	19.4
5,000-9,999		2	3.2
10,000-19,999		7	11.3
20,000-49,999		11	17.7
50,000-199,999		13	20.9
Unwilling to Answer/Don't Know		7	11.3

Table 37. Descriptive Statistics: MacArthur Subjective Status Scale (Cont)		
If You Subtracted All Debt (Credits, Unpaid Loans etc.) How Much Would You Have?	N=62	
<$500	28	45.2
500-4,999	6	9.7
5,000-9,999	4	6.5
20,000-199,999	6	9.6
Unwilling to Answer/Don't Know	18	29.0

Distress Composite Score

A score was developed to establish a single composite score of distress experienced during pregnancy. This created a single factor score for "distress" in Time 1 and Time 2. This "distress" composite score (representing generalized distress during pregnancy) was created using anxiety (STAI-state), depression (CES-D), perceived stress (PSS), mood disturbance (POMS-65), and sleep disturbance (PSQI duration). In the next section, the research questions and hypothesis testing will use the principal component analysis, which was used to create the single "Distress Composite Score".

Biological Variables

A blood sample for cytokine measures and hair sample for cortisol analysis were collected in the second and third trimesters of pregnancy. Levels of plasma IL-6 for T1 ranged from 0.20-4.12 pg/ml (N=87, M= 0.86, SD= 0.67), while T2 ranged from 0.19-2.22 pg/ml (N=61, M= 0.90, SD= 0.44). Levels of plasma TNF alpha for T1 ranged from 0.47-13.18 pg/ml (N=87, M= 1.67, SD= 1.72), while T2 ranged from 0.13-9.88 pg/ml (N=61, M= 1.43, SD= 1.50). The level of hair cortisol for T1 ranged from 1.10- 33.90 pg/mg (N=66, M= 7.11, SD= 5.29), while T2 ranged from 1.10-30.40 pg/mg (N=52, M= 7.82, SD= 4.70). Normative range for the R&D systems quantikine high sensitivity (HS)

Elisa (Minneapolis, MN) IL6 is .156 -10 pg/ml (serum EDTA Plasma Citrate Plasma), while the normative range for TNF alpha is .50-32 pg/ml (serum, EDTA plasma, heparin, Plasma, citrate plasma). The range of values for both IL-6 and TNF alpha are within this normative range with two values in the TNF alpha slightly below normative range. Hair cortisol mean normative range for Dr. Laudenslager's lab is 27 pg/mg, which in comparison, is higher than mean values in this study. This analysis was measured using ELISA high sensitivity kit, by Salimetrics and measured in Dr. Laudenslager's laboratory.

Examining descriptive statistics of the current study's biological variables revealed that each of them failed to show evidence of a normal distribution by both graphic illustration of the distribution and by the distance from zero (skewness and kurtosis < = 2.0) (Lewis-Beck, Bryman, & Liao, 2004). As a result, each biological variable was log transformed and achieved adequate normality after transformation. This is illustrated in Table 38. To ensure reliability in the study's parametric analysis, natural log transformed biological variables were used for all subsequent analyses.

Table 38. Descriptive Statistics: Biological Study Variables

	N	Mean	SD	Skewness	Kurtosis	Min.	Max.
IL-6 T1	87	0.86	0.67	3.12	12.11	0.20	4.12
Log IL-6 T1	87	-0.34	0.59	0.43	0.87	-1.61	1.42
IL-6 T2	61	0.90	0.44	1.19	1.47	0.19	2.22
Log IL-6 T2	61	-0.22	0.50	-0.44	0.84	-1.66	0.80
TNF Alpha T1	87	1.67	1.72	4.21	23.83	0.47	13.18
Log TNF Alpha T1	87	0.25	0.66	1.00	0.96	-0.75	2.58
TNF Alpha T2	61	1.43	1.50	3.99	18.91	0.13	9.88
Log TNF Alpha T2	61	0.09	0.69	0.42	2.27	-2.05	2.29
Hair Cortisol T1	66	7.11	5.29	2.85	11.14	1.10	33.90
Log Hair Cortisol T1	66	1.76	0.65	-0.24	1.16	0.10	3.52

Table 38. Descriptive Statistics of Biological Study Variables (cont.)

Hair Cortisol T2	52	7.82	4.70	2.29	9.55	1.10	30.40
Log Hair Cortisol T2	52	1.90	0.60	-0.59	1.27	0.10	3.41

Note: T1 represents the second trimester of pregnancy (16-24 weeks gestation); T2 represents the third trimester of pregnancy (28-32 weeks gestation); IL-6 and TNF alpha are in pg/ml; Hair cortisol is in pg/mg . All biologic variables were log transformed because they failed to show evidence of normal distribution. Once natural log transformed, these data met the requirements to for a normal distribution.

Specific Aims and Hypotheses (IRB Protocol)

Aim 1: Examine the relationship between maternal childhood adversity and maternal psycho-neuroendocrine-inflammatory (Kopnisky) profile during pregnancy.

Hypothesis 1. Maternal childhood adversity will be related to maternal psychosocial profile, higher levels of hair cortisol, and higher levels of plasma IL6 and TNF alpha during pregnancy.

Hypothesis 2. Maternal psychosocial profile during pregnancy will be related to higher levels of both maternal hair cortisol and plasma IL-6 and TNF-alpha.

Aim 2: Evaluate maternal risk and protective factors as moderators of maternal PNI profile during pregnancy.

Hypothesis 3. Maternal risk (income) and protective factors (social support) will moderate the relationship between maternal childhood adversity and:

a. Maternal PNI profile during pregnancy.

b. Neonatal outcomes.

Aim3: Explore the relationship among maternal childhood adversity, maternal PNI profile during pregnancy, and neonatal outcomes.

Hypothesis 4. Worse neonatal outcomes will be related to:

a. Greater maternal childhood adversity and altered PNI profile during pregnancy.
b. Higher maternal hair cortisol IL-6 and TNF-alpha levels during pregnancy.

Hypothesis Testing

Concerning Hypothesis 1—*Maternal childhood adversity will be related to maternal psychosocial profile, higher levels of hair cortisol, and higher levels of plasma IL6 and TNF alpha during pregnancy* —the following protocol was performed:

First a Pearson's r correlation coefficient was calculated to determine the relationship between each of the psychosocial variables. Next, a Pearson's r correlation coefficient was calculated to determine the relationship between maternal childhood adversity (CTQ) and psychosocial distress indices. These findings are illustrated in Tables 39, 40, and 50 below. Findings revealed that greater levels of maternal childhood adversity (total score) were significantly associated with higher scores on the Distress Composite Score as well as with higher levels of perceived stress (PSS), depression (EDS and CES-D), and anxiety (STAI), at T1; while greater levels of maternal childhood adversity (total score) was significantly associated with higher scores on Distress Composite Score, and higher levels of depression (CES-D), mood disorder POMS-65) at T2. [Note: the Distress Composite Scale is described below.] In contrast, greater levels of maternal childhood adversity were significantly related to lower levels of social

support at both T1 and T2. [Note: these correlations were corrected using a Bonferroni correction as listed in each of their respective tables.]

With respect to biological measures, findings revealed that maternal childhood adversity was not significantly correlated with hair cortisol concentration. In addition, no significant correlations were observed at either T1 or T2 between maternal childhood adversity and plasma levels of proinflammatory cytokines, IL-6 and TNF-alpha. Even when controlling for pre-pregnancy BMI using partial correlation, no significant associations were revealed between maternal childhood adversity and any of the biological measures at either T1 or T2; see Table 41.

Concerning Hypothesis 2—*Maternal psychosocial profile during pregnancy will be related to higher levels of maternal hair cortisol and higher levels of plasma IL-6 and TNF-alpha*—the following protocol was performed:

No significant correlation was found between the Distress Composite Score and levels of hair cortisol, evaluated at both T1 and T2. Further, hair cortisol levels were not correlated with perceived stress (PSS), depression (CES-D and EPDS), state anxiety (STAI), total mood disturbance (POMS-65), or global sleep (poor sleep) disturbance (PSQI), evaluated at both T1 and T2.

Findings revealed that the Distress Composite Score T1 and Distress Composite Score T2 did not correlate with TNF-alpha at T1 and T2, respectively. In addition, TNF alpha was not correlated with perceived stress (PSS), depression (CES-D and EPDS), state anxiety (STAI), total mood disturbance (POMS-65), or poor sleep (PSQI global sleep), at T1 or T2.

Table 39. Correlations (Pearson's r): Psychosocial Variables and Maternal Childhood Adversity Time 1

		PSS T1	EDS T1	CESD T1	POMS T1	STAI T1	SPA T1	PSQI Global T1
CTQ Total	r	.572*	.400*	.613*	.412	.494*	-.550*	258

*Bonferroni correction: p = <.007.

Table 40. Correlations (Pearson's r): Psychosocial Variables and Maternal Childhood Adversity Time 2

		PSS T2	EDS T2	CESD T2	POMS T2	STAI T2	SPA T2	PSQI Global T2
CTQ Total	r	.459	.389	.654*	.565*	.432	-.694*	229

*Bonferroni correction: p = <.007.

Table 41. Correlations (Pearson's r): Biological Variables and Maternal Childhood Adversity, Controlling for Pre-pregnancy BMI (only with proinflammatory cytokines)

	Plasma IL-6 T1	Plasma IL-6 T2	TNF-alpha T1	TNF-alpha T2	Hair Cortisol T1	Hair Cortisol T2
CTQ	-.023	.279	.051	.040	.058	.025
	n=39	n=30	n=39	n=30	n=41	n=34

CTQ=Child Trauma Questionnaire

*Bonferroni Correction: p<.008

**Correlation is significant at the 0.05 level (2-tailed).

Table 42. Correlations (Pearson's r): Biological Variables and Neonatal Birthweight and Gestational Age, Controlling for Pre-pregnancy BMI (only with proinflammatory cytokines)

	Plasma IL-6 T1	Plasma IL-6 T2	TNF-alpha T1	TNF-alpha T2	Hair Cortisol T1	Hair Cortisol T2
Birthweight	.026	-.080	-.182	-.295**	.126	.209

Table 42. Correlations (cont.)

Gestational age	.044	-.207	.006	-.181	.127	.200
	n=53	n=42	n=53	n=42	n=62	n=50

CTQ=Child Trauma Questionnaire

*Bonferroni Correction: p<.008

**Correlation is significant at the 0.05 level (2-tailed).

The following tables, Tables 43-48, display correlations of key stress variables with biological variables, at Time 1 and Time (T1 and T2), controlling for pre-pregnancy BMI.

Table 43. Correlations (Pearson's r): Key Psychosocial Variables and Plasma IL-6

Psychosocial Variable N=47	Plasma IL-6 T1	Psychosocial Variable N=27	Plasma IL-6 T2
PSS T1	-175	PSS T2	.051
EDS T1	-.128	EDS T2	.020
CES-D T1	-.159	CES-D T2	.321
POMS T1	-.257	POMS T2	.256
STAI T1	-.208	STAI T2	-.064
SPA T1	.154	SPA T2	-.284
PSQI T1	-.085	PSQI T2	-.146

T1= 2nd Trimester; T2=3rd Trimester; controlling for pre-pregnancy BMI was controlled

*Bonferroni Correction: p<.007

**Correlation is significant at the 0.05 level (2-tailed).

Table 44. Correlations (Pearson's r): Key Psychosocial Variables and Plasma TNF alpha

Psychosocial Variable N=64	Plasma TNF alpha T1	Psychosocial Variable N=43	Plasma TNF alpha T2
PSS T1	.184	PSS T2	-.158
EDS T1	.221	EDS T2	-.154
CES-D T1	.286**	CES-D T2	-.138
POMS T1	.049	POMS T2	.036
STAI T1	.120	STAI T2	-.181
SPA T1	.058	SPA T2	.107
PSQI T1	.217	PSQI T2	-.048

T1= 2nd Trimester; T2=3rd Trimester

*Bonferroni Correction: p<.007

**Correlation is significant at the 0.05 level (2-tailed).

Table 45. Correlations (Pearson's r): Key Psychosocial Variables and Hair Cortisol

Psychosocial Variable N=50	Hair Cortisol T1	Psychosocial Variable N=37	Hair Cortisol T2
PSS T1	.112	PSS T2	.018
EDS T1	.078	EDS T2	-.110
CES-D T1	-.018	CES-D T2	.059
POMS T1	-.087	POMS T2	-.078
STAI T1	-.067	STAI T2	-.149
SPA T1	.010	SPA T2	-.078
PSQI T1	.213	PSQI T2	.107

T1=2nd Trimester; T2=3rd Trimester

*Bonferroni Correction: p<.007

**Correlation is significant at the 0.05 level (2-tailed).

Table 46. Correlations (Pearson's r): CTQ Subscales and Proinflammatory Cytokine IL-6

Psychosocial Variable	Plasma IL-6 T1 n=39	Plasma IL-6 T2 n=30
Emotional Neglect	. 102	.346**
Emotional Abuse	-.031	.130
Physical Neglect	.075	.194
Physical Abuse	-.197	. 447*,**
Sexual Abuse	-.158	-.087

T1= 2nd Trimester; T2=3rd Trimester; controlling for pre-pregnancy BMI was controlled

*Bonferroni Correction: p<.01

**Correlation is significant at the 0.05 level (2-tailed).

Table 47. Correlations (Pearson's r): CTQ Subscales and Proinflammatory Cytokine TNF-alpha

Psychosocial Variable	Plasma TNF-alpha T1 n=39	Plasma TNF-alpha T2 n=30
Emotional Neglect	.019	.064
Emotional Abuse	-.078	-.016
Physical Neglect	.113	.183
Physical Abuse	.152	.033
Sexual Abuse	.076	-.130

T1= 2nd Trimester; T2=3rd Trimester; controlling for pre-pregnancy BMI was controlled

*Bonferroni Correction: p<.01

**Correlation is significant at the 0.05 level (2-tailed).

Table 48. Correlations (Pearson's r): CTQ Subscales and Hair Cortisol

Psychosocial Variable n=30	Hair Cortisol T1 n=41	Hair Cortisol T2 n=34
Emotional Neglect	.209	.158
Emotional Abuse	.014	-.017
Physical Neglect	.107	-.030
Physical Abuse	-.159	-.090
Sexual Abuse	-.031	.046

T1= 2nd Trimester; T2=3rd Trimester; controlling for pre-pregnancy BMI was controlled

*Bonferroni Correction: p<.01

**Correlation is significant at the 0.05 level (2-tailed).

Table 49. Correlations (Pearson's r): Distress Composite Score and Proinflammatory Cytokines (IL-6 and TNF Alpha), Controlling for Pre-pregnancy BMI

	Plasma IL-6 T1		Plasma IL-6 T2
Distress Composite Score T1 n=48	-227	Distress Composite Score T2 n=27	.110
	Plasma TNFalphaT1		Plasma TNFalphaT2
Distress Composite Score T1 n=48	.064	Distress Composite Score T2 n=27	-.086

T1= 2nd Trimester; T2=3rd Trimester; controlling for pre-pregnancy BMI was controlled

*Bonferroni Correction: p<.007

**Correlation is significant at the 0.05 level (2-tailed).

Table 50. Correlations (Pearson's r): Distress Composite Score and Hair Cortisol

	Hair Cortisol T1		Hair Cortisol T2
Distress Composite Score T1 n=42	.047	Distress Composite Score T2 n=28	-.017

T1= 2nd Trimester; T2=3rd Trimester

*Bonferroni Correction: p<.007

**Correlation is significant at the 0.05 level (2-tailed).

Distress Composite Score

A principal component analysis (PCA) was used create a single factor score for "stress" in Time 1 and Time 2. As stated earlier, this "Distress Composite Score" was created using anxiety (STAI-state), depression (CES-D), perceived stress (PSS), mood disturbance (POMS-65), and sleep disturbance (PSQI duration). In the next section, the research questions and hypothesis testing will use the principal component analysis as indicated.

Initially, an attempt to make an "Adversity Composite Score" using CTQ total score, SES (poverty variable), and social status (MacArthur Scale, rungs on a ladder) showed that these variables were uncorrelated with each other; and thus were unable to be combined to make a single construct. See inter-item correlation matrix below in Table 51.

Table 51. Inter-item Correlation Matrix: Adversity Composite Score

	Maternal Childhood Trauma	Rungs on a Ladder	Indicator of Poverty
Maternal Childhood Trauma	1.000	-.159	-.157
Rungs on a Ladder	-.159	1.000	-.079
Indicator of Poverty	-.157	-.079	1.000

Subsequently, a "distress composite score" (generalized distress) was created using anxiety (STAI-state), depression (CES-D), perceived stress (PSS), mood disturbance (POMS-65), and sleep disturbance (PSQI duration). Composite scores for second trimester (T1) and third trimester (T2) showed one factor was supported. Global sleep had the lowest percent of the variance explained but was maintained in the model.

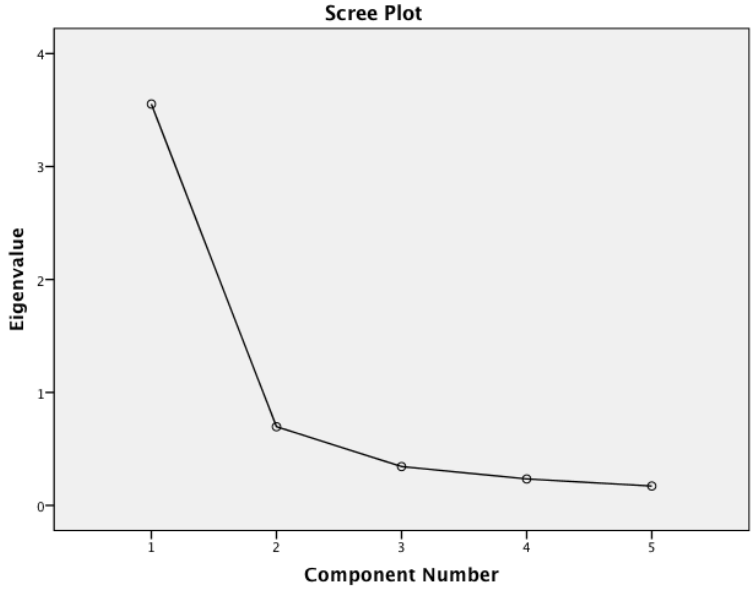


Figure 2. Scree plot Distress Composite Score 1.

Table 52. Component Matrix: Distress Composite Score 1

Component Matrix[a]

	Component 1
Perceived Stress T1	.887
General Depression T1	.918
General Anxiety T1	.887
Global_PSQI_T1	.616
Total Mood Disturbance T1	.870

Extraction Method: Principal Component Analysis.

[a]1 component extracted.

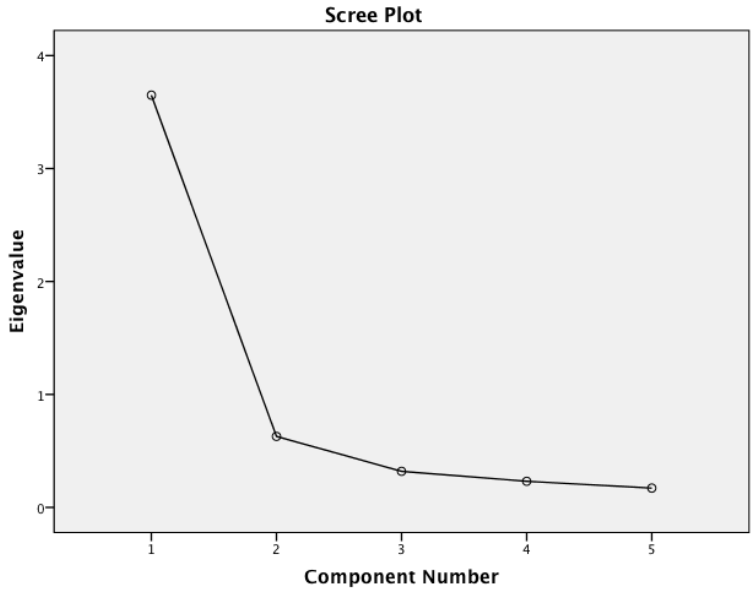


Figure 3. Scree plot Distress Composite Score 2.

Table 53. Component Matrix: Distress Composite Score 2

Component Matrix[a]

	Component
	1
Perceived Stress T2	.920
General Depression T2	.864
General Anxiety T2	.895
Global_PSQI_T2	.682
Total Mood Disturbance T2	.889

Extraction Method: Principal Component Analysis.
[a]1 component extracted.

The Distress Composite Score at T1 and T2 were highly correlated with maternal childhood adversity (CTQ) but not with birthweight, gestational age, pregnancy

complications, age, race dichotomous (recoded into White, non-White), or income; see Table 54 below.

Table 54. Correlations (Pearson's r): Distress Composite Scores, CTQ, and Other Variables

	CTQ	Birth Weight	Pregnancy Complications	Age	Race Dichotomous	Income
Distress Composite Score (T1)	.589*	-.194	-.114	-.069	-.043	.106
Distress Composite Score (T2)	.584*	-.230	.215	.009	.108	.261

T1=2nd Trimester; T2=3rd Trimester
* Bonferroni correction: p< .005

Income and Social Support as Moderators of Maternal PNI Profile

As noted earlier, Aim 2 was the following: *Evaluate maternal risk and protective factors as moderators of maternal PNI profile during pregnancy.* Hypothesis 3 of Aim 2 was the following:

Hypothesis 3. Maternal risk (income) and protective factors (social support) will moderate the relationship between maternal childhood adversity and:

a. Maternal PNI profile during pregnancy

b. Neonatal outcomes.

Income and Social Support as Moderators of Childhood Adversity on IL-6 and TNF alpha, and Hair Cortisol

Moderating effect of income on IL-6 at Time 1 and Time 2. Regressions analysis was used to determine if income level moderated the association between

childhood adversity and IL-6 at T1, while controlling for BMI at T1, race, and pregnancy complications. Biological variables IL-6, TNF alpha, and hair cortisol analysis were each log transformed prior to regression analysis to achieve a normal distribution. Possible control variables evaluated included pregnancy complications, race (as a dichotomous variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started. For this analysis, only those variables that were significantly correlated with childhood adversity or log IL-6 were included in the final regression model. Results indicated that of the control variables considered only BMI and race were significantly associated with IL-6 at T1 (beta= .06, p< .001, beta=.42, p=.025, respectively); thus, BMI and race were included in the final regression model. Results revealed that together with the covariates, income and childhood adversity predicted 45% of the variability in log IL-6 at T1; however, neither childhood adversity nor income were significant predictors of IL-6 at T1. Adding an interaction term of income by-childhood adversity explained an additional <1% of the variability in log IL-6 T1, which was not significant.

Further regression analysis was used to determine if income moderated the association between childhood adversity and log IL-6 T2 controlling for BMI at T1, race, and pregnancy complications. The results revealed income and childhood adversity predicted approximately 21% of the variability in log IL-6 T2 in the current sample, with neither childhood adversity nor income, significantly predicting log IL-6 T2. Adding an interaction term of income by-childhood adversity explained an additional 3% of the variability in log IL-6 T2, and was not significant.

Moderating effect of social support on IL-6 at Time 1 and Time 2. Next, regression analyses were used to determine if social support moderated the association between maternal childhood adversity and log IL-6 at T1 controlling for BMI at T1, race, and pregnancy complications. Results indicated that along with covariates, social support and childhood adversity predicted 48% of variability in log IL-6 T1. Social support and childhood adversity were not significant predictors. Adding an interaction term of social support by-childhood adversity explained an additional <1% of the variability in log IL-6 T1, which was not significant. From the covariates, BMI, and race were significantly associated with IL-6 T1 (p=.001, p=.02, respectively).

Finally, a regression analysis was used to determine if social support at T2 moderated the association between childhood adversity and log IL-6 at T2, controlling for BMI at T1, race, and pregnancy complications. Results indicated that social support and childhood adversity predicted 21% of variability in log IL-6 T2, along with other covariates. However, neither social support at T2 nor childhood adversity significantly predicted IL-6 at T2. Adding an interaction term of social support at T2-by-childhood adversity, explained an additional 3% variability in IL-6 at T2, however, this was not significant.

Moderating effect of income on TNF alpha at Time 1 and Time 2. First, regression analysis was used to determine if income level moderated the association between childhood adversity and log TNF alpha at Time 1. Potential control variables were first examined with respect to their relationship with childhood adversity and log TNF alpha. Decision was made to include only those variables that were significantly

associated with childhood adversity or TNF alpha. The possible control variables included pregnancy complications, race (as a dichotomous variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started. In this case, results indicated that none of the potential control variables were significantly associated with childhood adversity or TNF alpha; thus were included in the final model. Results of the regression analysis revealed that income and childhood adversity predicted approximately 8% of variability in TNF alpha at T1. Both childhood adversity and income were not statistically significant predictors of TNF alpha at T1. Adding an interaction term of income-by-childhood adversity explained an additional 1% of variability in TNF alpha T1, indicating that income was not a significant moderator of the association between childhood adversity and TNF alpha.

Further, regressions analysis was used to determine if income level moderated the association between childhood adversity and log TNF alpha at T2. Results indicated that income and childhood adversity predicted 5% of variability in TNF alpha T2 in the current sample; however, neither childhood adversity nor income significantly predicted TNF alpha at T2. Adding an interaction term of income-by-childhood adversity explained an additional <1% of variability in TNF alpha at T2, which was not significant. Thus, income was not a significant moderator of the association between childhood adversity and TNF alpha at Time 1 and Time 2.

Moderating effect of social support on TNF alpha at Time 1 and Time 2. Next a regression analysis was used to determine if social support moderated the association between childhood adversity and log TNF alpha. Results indicated that neither social

support nor childhood adversity significantly predicted TNF alpha at T1, explaining only 3% of the variability. Adding an interaction term of social support-by-childhood adversity explained an additional 1% of variability in TNF alpha T1, which was not significant.

Finally, a regressions analysis was used to determine if social support at T2 moderated the association between childhood adversity and log TNF alpha at T2. Results indicated that neither social support at T2 nor childhood adversity significantly predicted TNF alpha at T2, explaining only 7% of the variability in the current sample. Adding an interaction term of social support-by-childhood adversity explained an additional 2% of variability in TNF alpha at T2, which was not significant. Thus, social support was not a significant moderator of the association between childhood adversity and TNF alpha at Time 1 and Time 2.

Moderating effect of income on hair cortisol at Time 1 and Time 2. Regression analysis was used to determine if income moderated the association between childhood adversity and log hair cortisol at T1. Possible control variables assessed for this analysis included the following: pregnancy complications, race (as a dichotomous variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started. Feelings about pregnancy and race were significant, and thus were controlled for in the final models. The set of variables including childhood adversity and income explained 28% of variability in log hair cortisol T1; however neither of the variables were significant predictors. Adding an interaction term of

income-by-childhood adversity explained an additional 1% of the variability in log hair cortisol T1, which also was not significant.

Further, regression analysis was used to determine if income moderated the association between childhood adversity and log hair cortisol at T2 controlling for feelings about pregnancy and race. Results indicated that income and childhood adversity predicted approximately 16% of variability in log hair cortisol at T2 and neither childhood adversity, nor income, significantly predicted hair cortisol. Adding an interaction term of income-by-childhood adversity explained an additional <1% of the variability in log hair cortisol at T2, which was not significant.

Moderating effect of social support on TNF alpha at Time 1 and Time 2. Next, a regression analysis was used to determine if social support at T1 moderated the association between childhood adversity and hair cortisol at T1, while controlling for feelings about pregnancy and race. However, neither social support nor childhood adversity significantly predicted hair cortisol at T1, explaining 25% of the variability in the current sample. Adding an interaction term of social support-by-childhood adversity explained an additional <1% of variability hair cortisol T1, indicating that social support was not a significant moderator of the association between childhood adversity and hair cortisol at T1.

Finally, regression analysis was used to determine if social support moderated the association between childhood adversity and log hair cortisol at T2 while controlling for feelings about pregnancy and race. Results indicated that the control variables were not significantly associated with hair cortisol at T2. Additionally, neither social support nor

childhood adversity significantly predicted hair cortisol at T2, explaining 20% of the variability in the current sample. Adding an interaction term of social support-by-childhood adversity explained an additional <1% of variability hair cortisol at T2 indicating that social support was not a significant moderator of the association between childhood adversity and log hair cortisol at Time 2.

Income and Social Support as Moderators of Childhood Adversity on Neonatal Outcomes

Moderating effect of income on birthweight and gestational age. Regression analysis was used to determine if income level moderated the association between childhood adversity and birthweight. For this analysis, only variables that were significantly correlated with childhood adversity or birthweight were included in the final regression model. The possible control variables evaluated included pregnancy complications, race (as a dichotomous variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started. The results indicated that the control variable that assessed pregnancy complications was negatively and significantly associated with birthweight (beta=-.373, p=.05). In the final model, income level and child adversity predicted approximately 17% of variability in birthweight, with neither child adversity nor income significantly predicting birthweight. Adding an interaction term of income-by-childhood adversity explained an additional 1% of variability in birthweight, which was not significant.

Additionally, a regression analysis was used to determine if income moderated the association between childhood adversity and gestational age, while controlling for

pregnancy health care before pregnancy, feelings about pregnancy, and pregnancy complications. Results indicated that income and childhood adversity predicted approximately 13% of variability in gestational age in the current sample, with neither childhood adversity nor income significantly predicting gestational age. Adding an interaction term of income-by-childhood adversity explained an additional <1% of variability in gestational age, which was not significant.

Moderating effect of social support at Time 1 and Time 2 on birthweight and gestational age. Next, a regression analysis was used to determine if social support at T1 moderated the association between childhood adversity and birthweight while controlling for age, race (dichotomous), education, health care before pregnancy, planned pregnancy, feeling about pregnancy, and pregnancy complications. Results indicated that the control variables, pregnancy complications were significant predictors (or) in the model (N=43, beta= -.430.0, p=.02 respectively); these were significantly associated with birthweight. Results indicated that the variables including social support and childhood adversity predicted approximately 27% of variability in birthweight in the current sample, with neither childhood adversity nor social support mid-pregnancy significantly predicting birthweight. Adding an interaction term of social support at mid-pregnancy-by-childhood adversity explained an additional 2% of variability in birthweight, which was not significant.

Finally, a regressions analysis was used to determine if social support at T2 moderated the association between childhood adversity and birthweight controlling for age, race (dichotomous), education, health care before pregnancy, planned pregnancy,

feeling about pregnancy, and pregnancy complications. Results indicated that the control variables—feeling about pregnancy, planned pregnancy, pregnancy complications (beta= 418.1, p=.04, beta=-196.6 p=.03, beta= -214.6, p=.03 respectively)—were significantly associated with birthweight. In this model, social support and childhood adversity predicted approximately 38% of variability in birthweight in the current sample, with neither childhood adversity nor social support at mid-pregnancy significantly predicting birthweight. Adding an interaction term of social support-by-childhood adversity explained an additional 23% of variability in birthweight. The interaction term was significant (n=30, beta=1.5, p=. 004) indicating that social support moderated the effects of childhood adversity on birthweight. To further examine this interaction to understand the moderating effect of social support The Johnson-Neyman Technique was implemented (Hayes and Matthes, 2009). This technique computes the region of significance for the moderating variable, in this case social support. Results of the follow-up test revealed that values ≥ 86.7 on the social support questionnaire (i.e., Social Provision Scale) were demarcated as values that fall within the region of significance (at alpha=.05). That is, the conditional effect of childhood adversity on birthweight was statistically significant when the scores on the Social Provision Scale were above 86.7. In other words, those women with greater childhood adversity and greater social support (greater than 86.7) had higher birthweight babies than women with the same level of adversity but lower social support. In the present sample, 56.7% of the women responded with scores greater than 86.7.

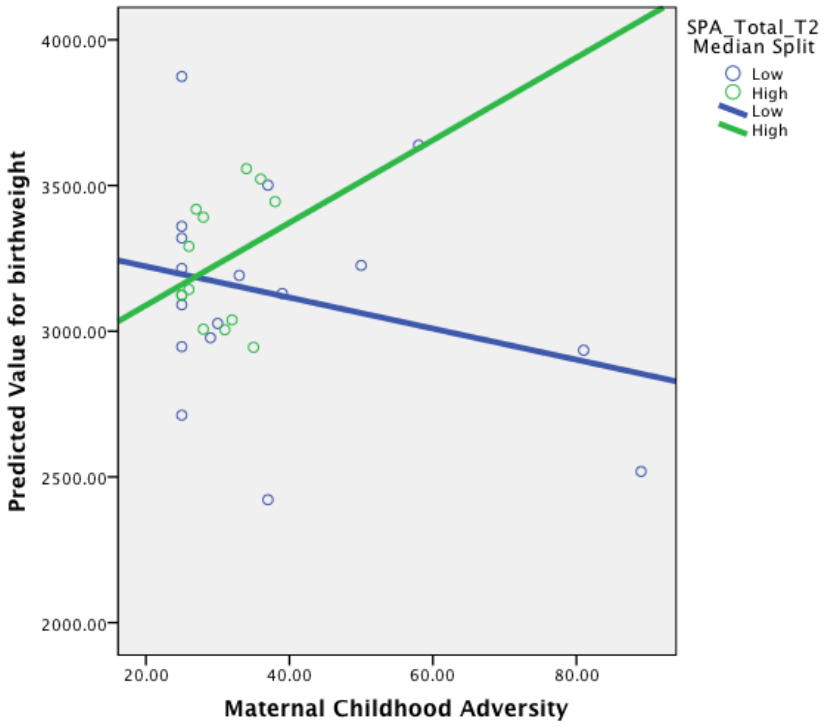


Figure 4. Impact of maternal childhood adversity on infant birthweight (N=43).

Therefore, social support buffers the negative impact of maternal childhood adversity on infant birthweight.

Regression analysis was used to determine if social support at T1 moderated the association between childhood adversity and gestational age, while controlling for age, race (dichotomous), education, planned pregnancy, feeling about pregnancy, and pregnancy complications. The results indicated that social support and childhood adversity predicted approximately 14% of variability in gestational age in the current sample, with neither childhood adversity nor social support late-pregnancy significantly predicting gestational age. Adding an interaction term of social support-late-pregnancy-by-childhood adversity explained an additional 3% of variability in gestational age, which was not significant.

Additionally, a regressions analysis was used to determine if social support at T2 moderated the association between childhood adversity and gestational age, controlling for age, race (dichotomous), education, planned pregnancy, feeling about pregnancy, and pregnancy complications. Results indicated that social support and childhood adversity predicted approximately 27% of variability in gestational age in the current sample, with neither childhood adversity nor social support late-pregnancy significantly predicting gestational age. Adding an interaction term of social support-late-pregnancy-by-childhood adversity explained an additional 24% of variability in gestational age, which was significant (N= 30, beta=.005, p=. 007). The Johnson-Neyman Technique was again utilized to further probe the significant interaction (Hayes and Matthes, 2009). Results of these follow-up analyses revealed that values ≤ 65.5 or values ≥ 87.6 were identified as points that defined the region of significance (at alpha=.05) of the effect of childhood adversity on gestational age. The conditional effect of childhood adversity was statistically significant when the scores on the social provision scale were either below 65.5 or above 87.6. In the present sample, approximately 7 % of the women had scores lower than 65.5 and 53% had scores greater than 87.6. As shown in Figure 6 (below) women with higher exposure to child adversity were more likely to deliver babies with higher gestational age if they also had greater social support (i.e., greater than 87.6) as compared to women who had low levels of social support (i.e., lower than 65.5). Thus, the harmful effects of maternal childhood adversity on gestational age are buffered in women with higher levels of social support.

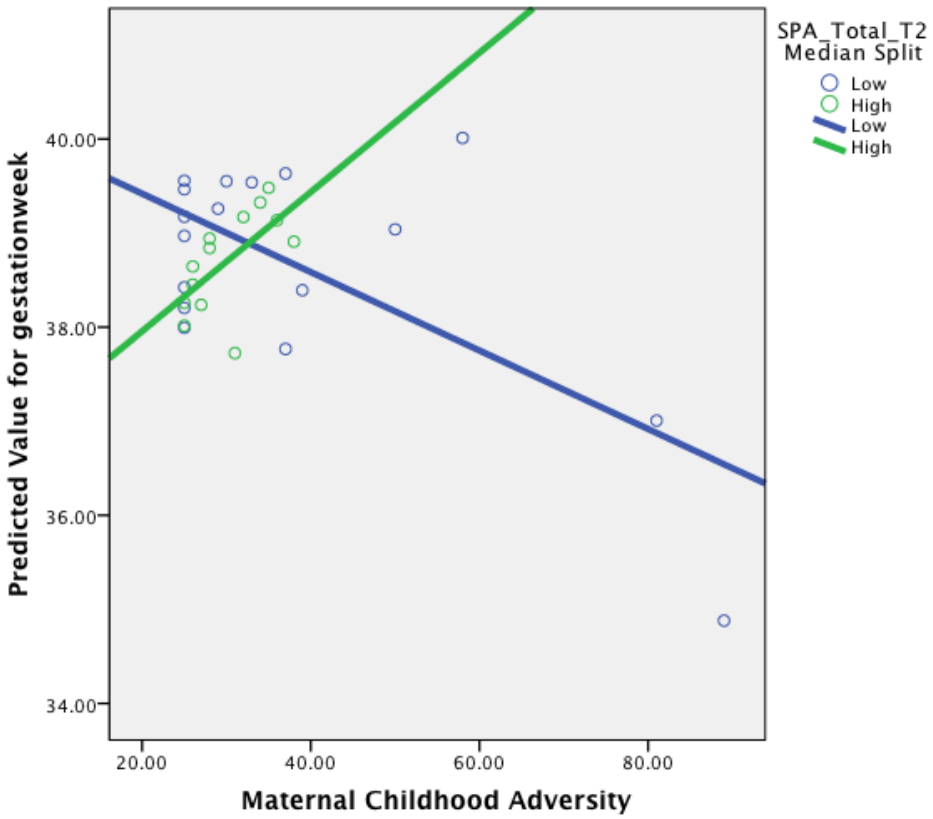


Figure 5. Harmful effects of maternal childhood adversity on gestational age (N=30).

Childhood Adversity as a Moderator of IL-6 at Time 1 and Time 2 on Infant Outcomes

As noted earlier, Aim 3 was the following: *Explore the relationship among maternal childhood adversity, maternal PNI profile during pregnancy, and neonatal outcomes*. Hypothesis 4 of Aim 3 was the following:

Hypothesis 4. Worse neonatal outcomes will be related to:

a. Greater maternal childhood adversity and altered PNI profile during pregnancy and neonatal outcomes; and
b. Higher maternal hair cortisol, IL-6 and TNF-alpha levels during pregnancy.

Hypothesis 4a. Pearson's r correlation coefficient was used to evaluate neonatal outcomes, both birthweight and gestational age with childhood adversity and psychosocial distress variables. Findings revealed that birthweight at T1 or T2 was not associated with maternal childhood adversity (total score), Distress Composite Score, perceived stress, depression (EDS and CES-D), anxiety (STAI), pregnancy specific anxiety (PAS), global sleep disturbance (PSQI), total mood disturbance (POMS-65), family dysfunction, or household global childhood abuse. Further, gestational age at T1 or T2 was not associated with maternal childhood adversity (total score), Distress Composite Score, perceived stress (PSS), depression (EDS), anxiety (STAI) pregnancy specific anxiety/distress (PAS and TPDS), global sleep disturbance (PSQI), total mood disturbance (POMS-65), family dysfunction and household global childhood abuse. However, gestational age was negatively correlated with depressive symptoms (CES-D at T2) ($r=-.30$, $p=.05$), but not at T1. Given that the correlational analyses were driven by an a priori hypothesis, no correction for familywise Type 1 error was used.

Hypothesis 4b. Using Pearson's r correlation coefficient, findings revealed that birthweight was positively correlated (approaching significance) with log hair cortisol at T2 ($r=.262$, $p=.07$) but not at T1. In contrast, gestational age was not correlated with log hair cortisol at T1 and T2. Further, no significant correlations were found between plasma TNF alpha (both non- and log-transformed values) and infant birthweight or gestational age at T1 or T2. Similarly, no correlations were found between levels of plasma IL-6 (both non- and log transformed) and infant birthweight or gestational age at T1 or T2.

Childhood adversity as a moderator of IL-6 at Time 1 and Time 2 on infant outcomes Regression analysis was subsequently used to determine if childhood adversity moderated the association between IL-6 at T1 and birthweight, controlling for BMI at T1, healthcare before pregnancy, feeling about pregnancy, and pregnancy complications. Of these covariates, only pregnancy complications were significantly related to birthweight (N=43, beta -458.74 p=. 02) and were therefore controlled in the final model. Results revealed that IL-6 at T1 and childhood adversity predicted approximately 21% of variability in birthweight, with neither childhood adversity nor IL-6 at T1 significantly predicted infant birthweight. Adding an interaction term of IL-6 at T1-by-childhood adversity explained an additional 4% of variability in birthweight, which was not significant.

Then, a regressions analysis was used to determine if IL-6 at T2 moderated the association between childhood adversity and birthweight, controlling for BMI at T1, healthcare before pregnancy, feeling about pregnancy, and pregnancy complications. Results indicated that IL-6 at T2 and childhood adversity predicted approximately 20% of variability in birthweight, with neither childhood adversity nor IL-6 at T2 significantly predicting birthweight. Adding an interaction term of IL-6 at T2-by-childhood adversity explained an additional 11% of variability in birthweight, which was significant (N=33, beta= -17.1, p=0.03).

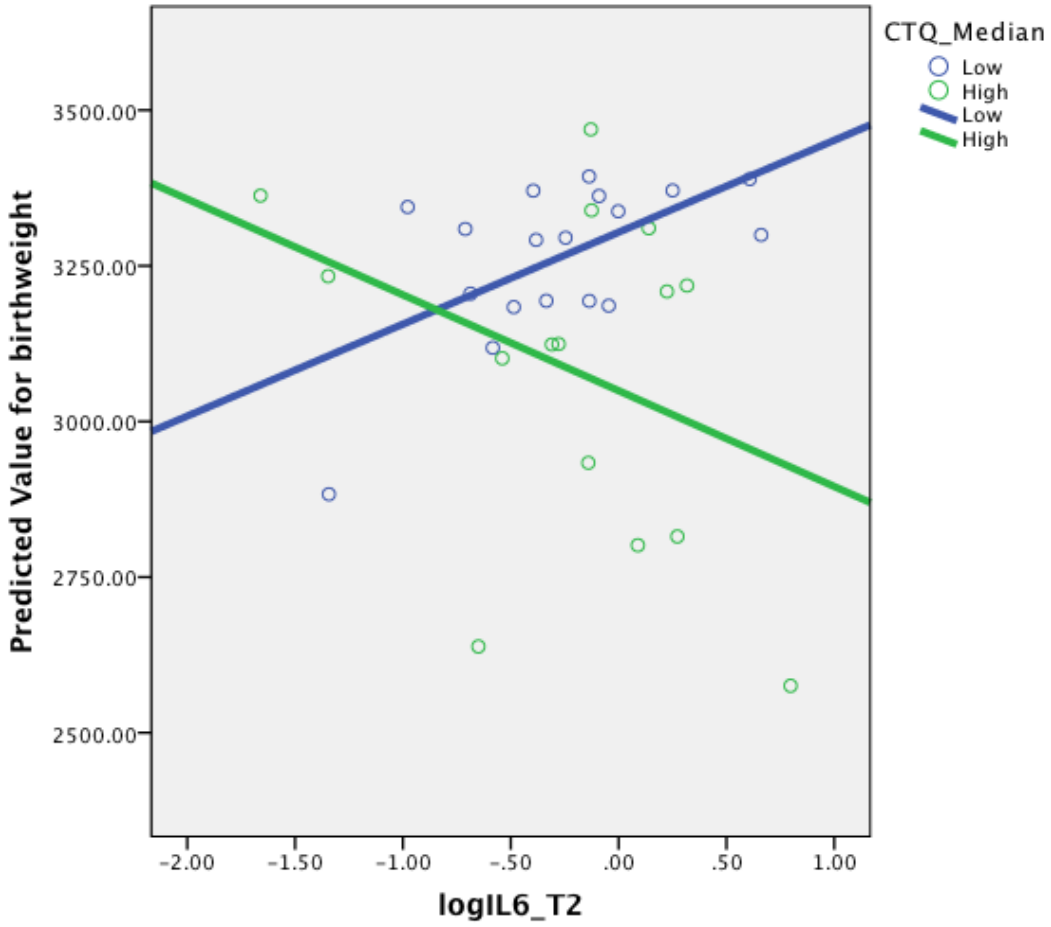


Figure 6. Childhood adversity interaction with plasma IL-6 levels: birth weight (N=33).

The Johnson-Neyman technique to probe the significant interaction indicated that women who scored greater than 58.1("58.1 and above" was defined as a point of the region of significance at alpha = .05) on the Childhood Trauma Questionnaire (CTQ) were at a significantly greater risk to have lower birthweight babies if they also had greater IL-6 at T2. In the present sample, 6% of women scored greater than the boundary for the region of significance. In sum, childhood adversity interacted with plasma IL-6 levels, such that greater exposure to childhood adversity and higher IL-6 levels predicted lower birthweight. (N=33, beta= -17.1, p=0.03).

Next, a regression analysis was used to determine if childhood adversity moderated the association between IL-6 at T1 and gestational age, controlling for BMI at T1, healthcare before pregnancy, feeling about pregnancy, and pregnancy complications. Results indicated that IL-6 at T1 and childhood adversity predicted approximately 12% of variability in birthweight in the current sample, with neither childhood adversity nor IL-6 at T1 significantly predicting gestational age. Adding an interaction term of IL-6 at T1-by-childhood adversity explained an additional 1% of variability in gestational age, which was not significant.

Finally, a regression analysis was used to determine if childhood adversity moderated the association between IL-6 at T2 and gestational age, controlling for BMI at T1, health care before pregnancy, feeling about pregnancy, and pregnancy complications. The results indicated that childhood adversity and IL-6 T2 predicted approximately 21% of variability in gestational age in the current sample, with childhood adversity (N=33, beta=-.036, p=. 056)—but not IL-6 T2—significantly predicting gestational age. Adding an interaction term of IL-6 at T2-by-childhood adversity explained an additional 15% of variability in gestational age, which was significant (N=33, beta= -.07, p=0.02). The Johnson-Neyman technique to probe the significant interaction indicated that women who scored greater than 51.1 ("51.1 and above" was defined as a point of the region of significance at alpha = .05) on the Childhood Trauma Questionnaire (CTQ) were at a significantly greater risk to have lower gestational age babies if they also had greater IL-6 at T2. In the present sample, 9% of women scored greater than the boundary for the region of significance.

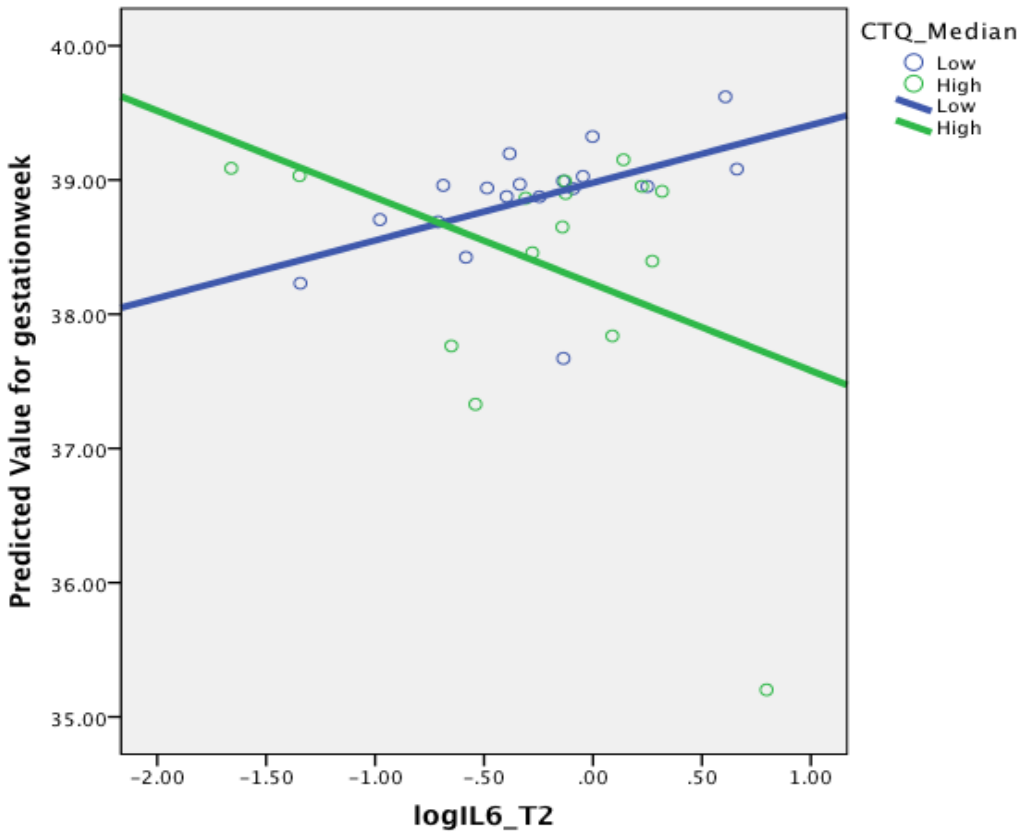


Figure 7. Childhood adversity interaction with plasma IL-6 levels: gestational age (N=33).

Childhood adversity interacted with plasma IL-6 levels such that greater exposure to childhood adversity and higher IL-6 levels predicted earlier gestational age. That is, women who experienced higher levels of maternal childhood adversity and who had higher levels of plasma IL-6 delivered infants at earlier gestational age (N=33, beta= -.07, p=0.02).

Childhood adversity as a moderator of TNF alpha at Time 1 and Time 2 on infant outcomes. Regression analysis was then used to determine if childhood adversity moderated the association between log TNF alpha T1 and birthweight. For this analysis, possible control variables that were evaluated included pregnancy

complications, race (as a dichotomous variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started; and only those variables that were significantly correlated with childhood adversity or birthweight were included in the final regression models. Results indicated that the control variable that assessed pregnancy complications significantly predicted birthweight (N= 44, beta=-446.0, p=.02), such that greater pregnancy complications were associated with lower birthweight. Log TNF alpha at T1 and childhood adversity predicted approximately 19% of variability in birthweight in the current sample, with neither childhood adversity nor TNF alpha T1 significantly predicting birthweight. Adding an interaction term of log TNF alpha at T1-by-childhood adversity explained an additional 3% of variability in birthweight, which was not significant.

Additionally, a regression analysis was used to determine if childhood adversity moderated the association between log TNF alpha at T2 and birthweight, controlling for feelings about pregnancy, healthcare before pregnancy, and pregnancy complications. Results indicated that log TNF alpha T2 and childhood adversity predicted approximately 20% of variability in birthweight in the current sample, with neither childhood adversity nor TNF alpha T2 significantly predicting birthweight. Adding an interaction term of log TNF alpha T2-by-childhood adversity explained an additional 2% of variability in birthweight, which was not significant.

Next, a regression analysis was used to determine if childhood adversity moderated the association between log TNF alpha T1 and gestational age. The possible control variables evaluated included pregnancy complications, race (as a dichotomous

variable, White, Non-White), planned pregnancy, feelings about pregnancy multiparas, and week prenatal care started; only health care before pregnancy, feelings about pregnancy, and pregnancy complications were significant control variables. The results indicated that log TNF alpha at T1 and childhood adversity predicted approximately 8% of variability in gestational age in the current sample, with neither childhood adversity nor TNF alpha at T1 significantly predicting gestational age. Adding an interaction term of log TNF alpha at T1-by-childhood adversity explained an additional 3% of variability in gestational age, which was not significant.

Finally, a regression analysis was used to determine if childhood adversity moderated the association between log TNF alpha T2 and gestational age. Results indicated that log TNF alpha at T2 and childhood adversity predicted approximately 20% of variability in gestational age in the current sample, with neither childhood adversity gestational age but not TNF alpha at T2, significantly predicting gestational age. Adding an interaction term of log TNF alpha at T2-by-childhood adversity explained an additional <1% of variability in gestational age, which was not significant.

Childhood adversity as a moderator of the effects of hair cortisol on infant outcomes. Regression analysis was used to determine if childhood adversity moderated the association between log hair cortisol at T1 and birthweight controlling for race dichotomous (recoded into White, non-White), health care before pregnancy, feelings about pregnancy, pregnancy complications. Results indicated that childhood adversity and log hair cortisol at T1 predicted approximately 9% of variability in birthweight in the current sample, while neither childhood adversity nor hair cortisol at

T1 significantly predicting birthweight. Adding an interaction term of log hair cortisol at T1-by-childhood adversity explained an additional <1% of variability in birthweight, which was not significant.

Additionally, a regression analysis was used to determine if childhood adversity moderated the association between log hair cortisol at T2 and birthweight. Results indicated that log hair cortisol at T2 and childhood adversity predicted approximately 11% of variability in birthweight in the current sample, with neither childhood adversity nor hair cortisol T2 significantly predicting birthweight. Adding an interaction term of log hair cortisol at T2-by-childhood adversity explained an additional 15% of variability in birthweight, which was significant (N=28: race dichotomous: White 15, non-White 13, beta= 29.33, p= .05). The Johnson-Neyman technique was used to further explore the moderating effects of childhood adversity on the relationship between hair cortisol and birthweight. Results identified values on the Childhood Trauma Questionnaire (CTQ) equal or above 51.9 as a boundary for the region of significance (at alpha = .05). In the present sample, 10% of women scored greater than this boundary.

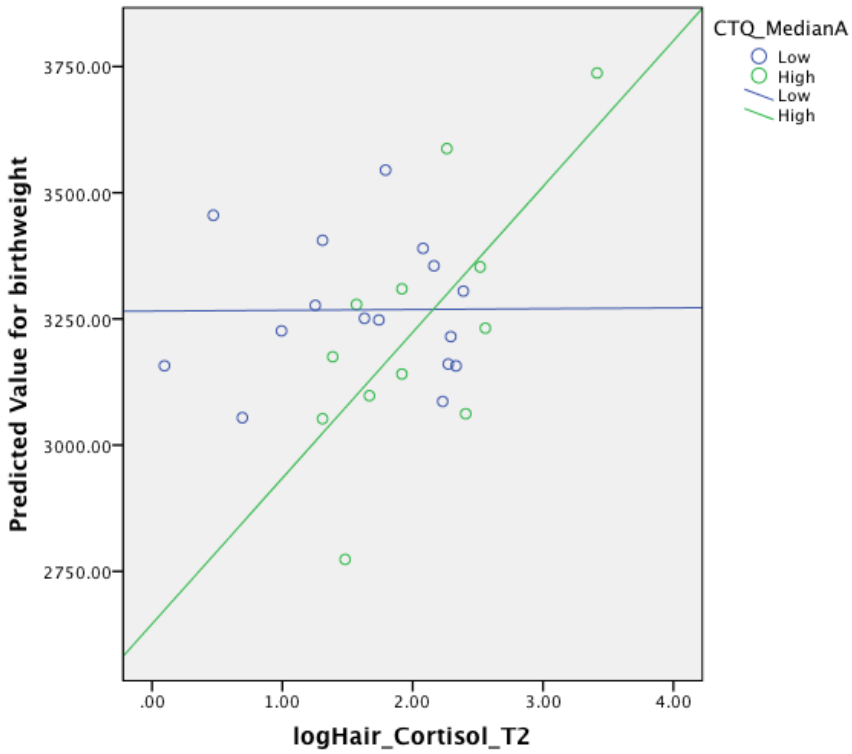


Figure 8. Childhood adversity interaction with hair cortisol levels at T2: birth weight (N=28).

As seen in Figure 8, childhood adversity interacted with hair cortisol levels at T2, such that women exposed to high levels of childhood adversity in combination with higher hair cortisol had infants with greater birthweight. In contrast, women in late pregnancy with lower childhood adversity had no association between hair cortisol and birthweight (N=28: White 15, non-White 13, beta= 38.43, p= .02). Given the small sample size in this analysis, caution should be used in its interpretation. It is contrary to what was hypothesized.

Next, a regression analysis was used to determine if childhood adversity moderated the association between log hair cortisol at T1 gestational age. Results indicated that childhood adversity and log hair cortisol at T1 predicted approximately

13% of variability in gestational age in the current sample, with neither childhood adversity nor hair cortisol at T1 significantly predicting gestational age. Adding an interaction term of log hair cortisol at T1-by-childhood adversity explained an additional <1% of variability in gestational age, which was not significant.

Finally, a regression analysis was used to determine if childhood adversity moderated the association between log hair cortisol at T2 and gestational age. Results indicated that log hair cortisol at T2 and childhood adversity predicted approximately 25% of variability in gestational age in the current sample, with neither childhood adversity nor hair cortisol at T2 significantly predicting gestational age. Adding an interaction term of log hair cortisol atT2-by-childhood adversity explained an additional 24% of variability in gestational age, which was significant (N=28, race dichotomous, White 15, non-White 13, beta= .10, p= .04). The Johnson-Neyman technique was used to further explore the moderating effects of childhood adversity on the relationship between hair cortisol and gestational age. Values on the Childhood Trauma Questionnaire (CTQ) equal or above 50.5 defined the boundary for the region of significance (at alpha = .05). In the present sample, 10% of women scored greater than this boundary.

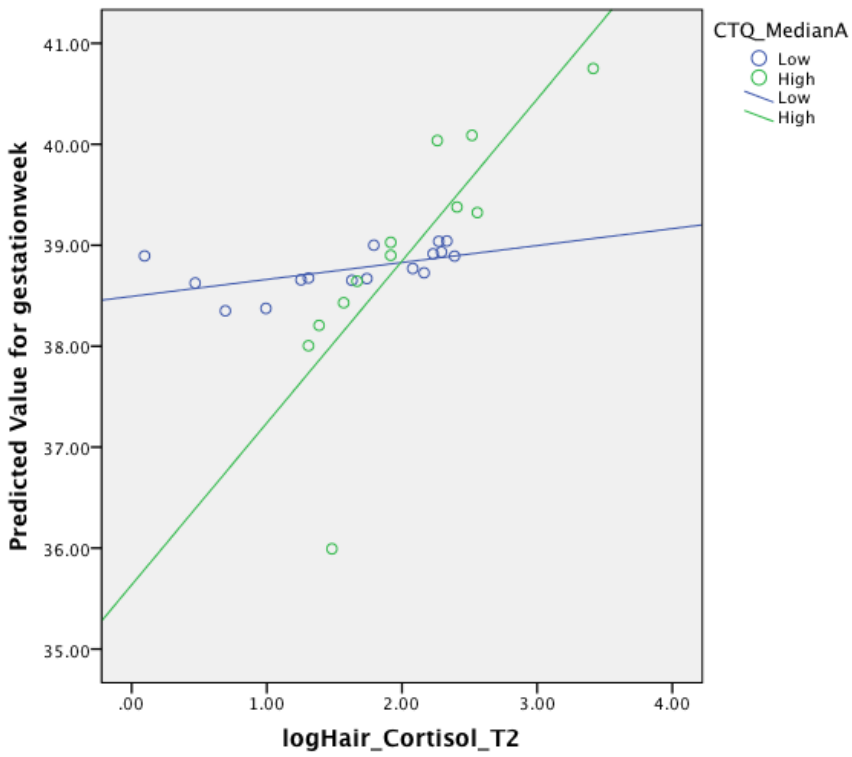


Figure 9. Childhood adversity interaction with hair cortisol at T2: gestational age (N=28).

As seen in Figure 9 (above) women in the late pregnancy with higher childhood adversity had a positive relationship between hair cortisol and gestational age, whereas women in late pregnancy with lower childhood adversity had no association between hair cortisol and gestational age. Given the small sample size (N=28) in this analysis, caution should be used in its interpretation. It is contrary to what was hypothesized.

Also it should be noted that no correction for the familywise Type 1 error was applied as all of the analyses were performed based on theory-driven a priori hypotheses.

Post Hoc Evaluation

In the post hoc evaluation, first CTQs subscales were evaluated to determine what specific subscales were associated with the key biological and psychological variables. Bonferonni correction was used to control for the familywise Type 1 error. Accordingly,

alpha level for the following analyses was set at .005. When looking at the CTQ total and subscales, only emotional neglect and physical abuse were correlated with IL6 at T2 (N= 30 r=.346, p= .05, N= 30 r= .447, p= .01, respectively). None of the other subscales (emotional abuse, physical neglect, or sexual abuse) were correlated with the biologic variables (IL6, TNF alpha or hair cortisol). For psychological variables, the CTQ total and each of the subscales were correlated with perceived stress at T1 and T2, while approaching significance on sexual abuse at both T1 and T2. Both the CTQ total and each of the subscales, except on sexual abuse, were highly correlated with depression risk measures (CESD and EDS) at both. Additionally, state anxiety (STAI) at T1 was highly correlated with total CTQ and all subscales, except for sexual abuse. Further, anxiety (STAI) at late pregnancy, physical abuse and neglect were highly correlated with total CTQ, while emotional neglect approached significance; while both sexual abuse and emotional abuse were not correlated with CTQ subscales (see Table 55 below). These positive associations suggest that the subscales may provide additional information regarding the impact of emotional and physical neglect and abuse, in addition to sexual abuse, which influence the impact of stressors across pregnancy.

Table 55. Correlations: Key Distress Variables with CTQ Subscales with PSS

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
PSS T1	r	.472*	.483*	.565*	.436*	.257
PSS T2	r	.355	.352	.426	.468	.318

* Bonferroni Correction p <.005

Table 56. Correlations: Key Distress Variables with CTQ Subscales with CES-D

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
CESD T1	r	.511 *	.484*	.655*	.493*	.212
CESD T2	r	.623*	.517 *	.574*	.635*	.236

* Bonferroni Correction p< .005

Table 57. Correlations: Key Distress Variables with CTQ Subscales with EDS

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
EDS T1	r	.356	.335	.408	.289	.123
EDS T2	r	.348	.248	.406	.371	.239

* Bonferroni Correction p< .005

Table 58. Correlations: Key Distress Variables with CTQ Subscales with STAI

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
STAI T1	r	.433*	.408*	.410*	.387	.291
STAI T2	r	.344	.299	.458	.470	.209

* Bonferroni Correction p < .005

Table 59. Correlations: Key Distress Variables with CTQ Subscales with POMS-65

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
POMS T1	r	.349	.361	.281	.406	.245
POMS T2	r	.543*	.439	.569*	.558*	.125

* Bonferroni Correction p< .005

Table 60. Correlations: Key Distress Variables with CTQ Subscales with PSQI

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
PSQI T1	r	.331	.162	.290	.168	-.06
PSQI T2	r	.293	.099	.264	.141	-.129

* Bonferroni Correction p< .005

Table 61. Correlations: Key Distress Variables with CTQ Subscales with SPA

		Emotional Neglect	Emotional Abuse	Physical Neglect	Physical Abuse	Sexual Abuse
SPA T1	r	-460*	-.393	-.597*	-.427*	-.288
SPA T2	r	-.651*	-.502*	-.740*	-.649*	-.235

* Bonferroni Correction p < .005

Group Differences in Stressors, Depression, Anxiety and Social Support, for Low versus High Income Women

In the post hoc evaluation, independent t-test was used to evaluate differences in stressors in low versus high-income women as illustrated in Table 62. In this sample, women with low income had differences in mean psychological variables compared to women with higher income. Specifically, women with lower income had greater mean scores on depression (CESD T1), and lower mean scores on social support (SPA T1). Further, women that were economically disadvantaged had greater depression (risk), anxiety, and lower social support across pregnancy. Bonferonni correction was used to control for the familywise Type 1 error was set at p< .005.

Table 62. Differences in Psychological Variables in High versus Low Income Women: Income (Cut Score) and Psychological Distress Variables

	Below 60K Income			Above 60K Income				Effect Size
	N	M	SD	N	M	SD	t-test	(d)
EDS T1	31	8.0	5.8	33	5.5	3.4	t(61)=2.54	.74
EDS T2	20	5.9	4.8	22	3.5	2.9	t(40)=1.95	.70
CESD T1	31	17.1	12.9	30	8.9	9.5	t(62)=2.90*	.78
STAI T1	31	40.7	13.9	33	32.4	10.9	t(62)=2.66	.68
STAI T2	18	39.9	13.6	21	30.0	9.7	t(39)=2.64	.86
SPA T1	31	79.9	11.5	33	88.7	6.9	t(62)=3.68*	1.06
SPA T2	20	83.8	9.3	21	89.8	9.3	t(39)=2.07	.66

Perceived Stress Scale (PSS); Edinburgh Depression Scale (EDS); Center for Epidemiologic Studies Depression Scale (CESD); State-Trait Anxiety Inventory (STAI); Profile of Mood States – Mood Disturbance (POMS-65); Childhood Trauma Questionnaire (CTQ); Maternal childhood adversity; Social Provisions Scale – Social Support (SPA);
Income Cut Off = $60,000/year (60K)
* Bonferroni Correction P>. 005
Effect size d= range 0-2; .2=small, .5=medium, .8=large.

Social support is important during pregnancy. Therefore, social support was investigated looking at differences in women above and below the cut score based on normative mean values. An independent t-test revealed that perceived stress (PSS) at T1 was significantly higher for pregnant women with social support levels below the cut score than for women above cut score (see Table 63). An independent t-test revealed that at mid-pregnancy there were mean differences in perceived stress (PSS), depression (CES-D) anxiety (STAI) and mood disorder (POMS-65) in pregnant women with low social support (below the cut score) than for women with high social support (above the cut score). Bonferonni correction was used to control for the familywise Type 1 error was set at .008.

Table 63. Differences in Psychological Variables in High versus Low Social Support

	Low Social Support T1			High Social Support T1				Effect
	N	M	SD	N	M	SD	t-test	Size (d)
PSS T1	12	24.5	8.2	52	14.3	5.6	t(62)=5.27*	1.34
EDS T1	12	11.3	6.6	51	5.7	3.7	t(61)=2.89	1.62
CESD T1	12	29.6	13.6	52	9.1	7.4	t(62)=5.04*	2.85
STAI T1	12	53.8	10.2	52	32.5	10.0	t(62)=6.54*	3.25
POMS-65 T1	8	56.3	35.7	45	13.9	15.5	t(51)=3.29*	2.40
CTQ	9	47.3	24.0	36	30.5	6.3	t(43)=2.08	1.45

Perceived Stress Scale (PSS); Edinburgh Depression Scale (EDS); Center for Epidemiologic Studies Depression Scale (CESD); State-Trait Anxiety Inventory (STAI); Profile of Mood States – Mood Disturbance (POMS-65); Childhood Trauma Questionnaire (CTQ); Maternal childhood adversity; Social Support Cut Score >78;
* Bonferroni Correction P<.008
Effect size d= range 0-2; .2=small, .5=medium, .8=large.

Women with higher maternal childhood adversity with greater CTQ scores had greater depression (EDS T1), anxiety (STAI T1), and lower social support (SPA T1 and T2, approaching significance) using uncorrected correlations.

Post-hoc analysis was conducted to determine differences in psychological variables in women stratified into high versus low childhood adversity (using median split). As illustrated in Table 64, women who had higher exposure to childhood adversity reported significantly higher levels of depression at mid-pregnancy (EDS). Bonferonni correction was used to control for the familywise Type 1 error was set at .008.

Table 64. Differences in Psychological Variables in High versus Low Maternal Childhood Adversity (CTQ)

	Low CTQ			High CTQ				Effect
	N	M	SD	N	M	SD	t-test	Size (d)
PSS T1	23	14.3	5.3	22	18.6	9.1	t(43)=1.96	1.03
EDS T1	22	5.0	.7	22	9.2	5.8	t(33)=2.95*	.68
CESD T1	23	10.7	8.2	22	17.7	15.2	t(32)=1.92	.67
STAI T1	23	33.4	10.4	22	42.0	16.1	t(36)=2.01	.62
SPA T1	23	86.0	7.7	22	80.1	13.6	t(33)=1.78	.62
SPA T2	17	88.9	5.1	15	81.8	13.6	t(17)=1.91	.92

Perceived Stress Scale (PSS); Edinburgh Depression Scale (EDS); Center for Epidemiologic Studies Depression Scale (CESD); State-Trait Anxiety Inventory (STAI); Profile of Mood States – Mood Disturbance (POMS-65); Childhood Trauma Questionnaire (CTQ); Maternal childhood adversity; Social Provisions Scale – Social Support (SPA);
Maternal Childhood Adversity Cut Score = Scale Median
* Bonferroni Correction P<.008
Effect size d= range 0-2; .2=small, .5=medium, .8=large.

Post Hoc Analysis:

Childhood Adversity as a Moderator of the Distress Composite Score on Infant Outcomes

A regressions analysis was used to determine if childhood adversity moderated the association between the Distress Composite Score at T1 and birthweight, controlling for BMI at T1, race as dichotomous variable, and pregnancy complications. Results indicated that the Distress Composite Score at T1 and childhood adversity predicted approximately 34% of variability in birthweight in the current sample, with Distress Composite Score T1 and pregnancy complications, significantly predicting birthweight (N=35, beta=-277.63, p=.04, beta=-660.18, p=.002, respectively) while maternal childhood adversity did not predict birthweight. Adding an interaction term of Distress Composite Score T1-by-childhood adversity explained an additional 5% of variability in birthweight, which was not significant. For further clarification, there were significant

and negative main effects of Distress Composite Score T1 and pregnancy complications on birthweight but not an interaction with childhood adversity.

Finally, a regression analysis was used to determine if childhood adversity moderated the association between the Distress Composite Score at T2 and birthweight, controlling for BMI at T1, race as a dichotomous variable, and pregnancy complications. Results indicated that the Distress Composite Score at T2 and childhood adversity predicted approximately 13% of variability in birthweight in the current sample, but this was not significant. Adding an interaction term of Distress Composite Score T2-by-childhood adversity explained an additional 24% of variability in birthweight, which was significant (N= 23, beta= -14.71, p=.02). The Johnson-Neyman post hoc analyses revealed that for women who scored greater than 56.3 on the Childhood Trauma Questionnaire (approximately 10% of the present sample), the negative relationship between Distress Composite Score and birthweight was significant. That is, women who had higher Distress Composite Score were more likely to deliver lower birthweight babies if they reported greater exposure to childhood adversity (≥56.3).

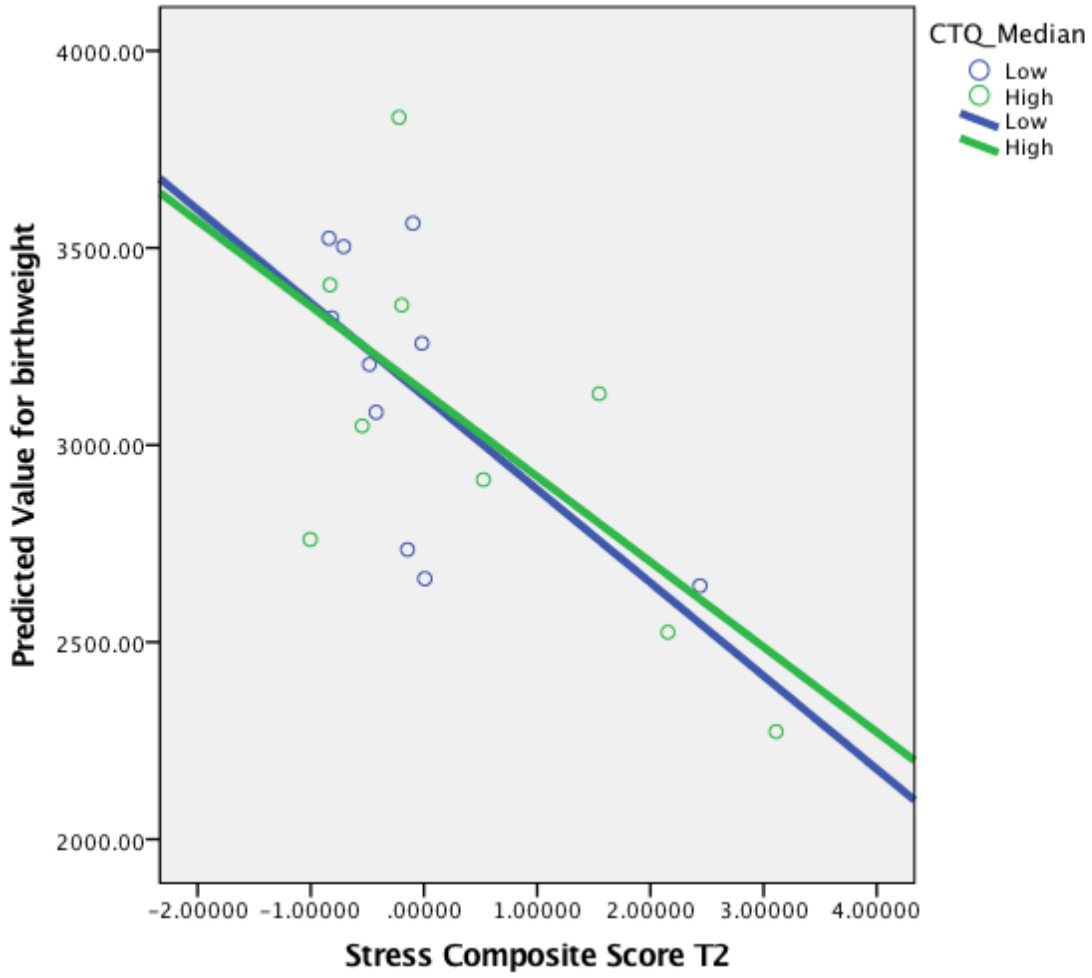


Figure 10. Post hoc analysis, showed a negative relationship between Distress Composite Score in late-pregnancy and birth weight (N=23).

Similarly, There were no main or interaction effects when looking at the regressions analysis used to determine if childhood adversity moderated the association between Distress Composite Score T1 and gestational age, while controlling for BMI at T1, race (dichotomous variable), and pregnancy complications. There were no main effects of interaction between Distress Composite Score T1 and maternal childhood adversity. Results indicated that Distress Composite Score T1 and childhood adversity

predicted approximately 22% of variability in gestational age in the current sample, with pregnancy complications, significantly predicting gestational age (beta=-1.85, p=.04) while Distress Composite Score T1, and maternal childhood adversity did not predict gestational age. Adding an interaction term of Distress Composite Score T1-by-childhood adversity explained an additional 2% of variability in gestational age, which was not significant.

Finally, there were no main effects but an interaction effect between the moderator, maternal childhood adversity, and Distress Composite Score at T2, and infant gestational age, controlling for BMI at T1, race as dichotomous variable, and pregnancy complications. Results indicated that Distress Composite Score at T2 and childhood adversity predicted approximately 36% of variability in gestational age in the current sample, with Distress Composite Score at T2 and maternal childhood adversity did not predict predicting gestational age. Adding an interaction term of Distress Composite Score at T2-by-childhood adversity explained an additional 24% of variability in gestational age, which was significant (N=23, beta= -.036, p=.04). The Johnson-Neyman post hoc analyses revealed that for women who scored greater than 49.4 on the Childhood Trauma Questionnaire (approximately 13% of the present sample), the negative relationship between Distress Composite Score and birthweight was significant. That is, women who had higher Distress Composite Score were more likely to deliver lower gestational age babies if they reported greater exposure to childhood adversity ($\geq$49.4).

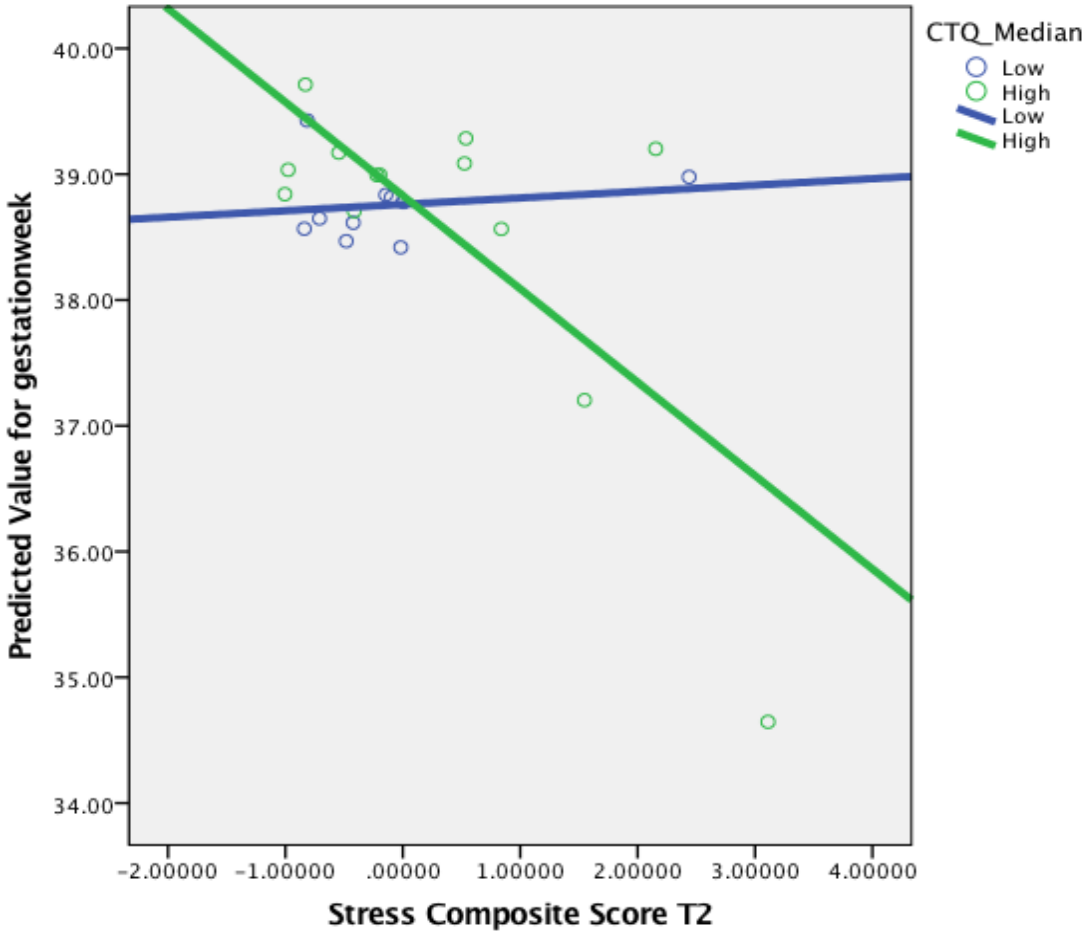


Figure 11. Post hoc analysis, showed a negative relationship between Distress Composite Score at Time 2 and gestational age (N=23)

Thus, there is a negative relationship between Distress Composite Score at T2 and gestational age in women with high maternal childhood adversity, whereas this effect is not apparent with women with low childhood adversity. Maternal childhood adversity moderated the relationship between the Distress Composite Scores and infant gestational age, such that women with greater childhood adversity and higher Distress Composite Score at T2 delivered infants with lower gestational age (i.e., earlier delivery).

CHAPTER FIVE

DISCUSSION

Introduction

The overall purpose of this chapter is to discuss key study findings, convergence and divergence from previous research, and implications for the health of pregnant women and their newborns. A successful pregnancy is vital to the health of future generations, and research to improve maternal infant health, including psychological well-being, is a national priority (People, 2011). Yet maternal-child outcomes can be jeopardized by a variety of environmental influences. Evolving evidence suggests that exposure to maternal stressors and mood disturbance negatively impact maternal mental health, birth outcomes, and subsequent child development (de Weerth & Buitelaar, 2005; Diego et al., 2006; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). However, the underlying biological mechanisms are poorly understood. Further, little is known about the effect of prior life (antenatal) adversity on psychological, neuroendocrine and inflammatory responses of women who face the adaptive challenges inherent to pregnancy and anticipation of parenting.

The overarching objective of this project was to evaluate the influence of a woman's history of childhood adversity on her psychological, neuroendocrine, and

proinflammatory profile during her pregnancy. In addition, the effect of maternal childhood adversity on infant outcomes was evaluated.

The central hypothesis was that *adverse childhood experiences prior to pregnancy prime stress response systems, leading to greater psychological distress, neuroendocrine activation, and dysregulated proinflammatory cytokine levels*. Such alterations in maternal stress-response systems may contribute to poor infant outcomes. It is anticipated that the results of this investigation will have the potential to positively impact maternal-infant health, by contributing to better identification of antenatal psychosocial risk that portend poor maternal-child health outcomes.

Summary of Key Study Findings

Psychological Status

Women enrolled in this study reported elevated levels of stress perception, with 63% and 52% scoring above the normative mean value for the PSS at mid-pregnancy (T1) and late pregnancy (T2), respectively. Forty-one percent of women reported high levels of state anxiety at mid-pregnancy, while only 24% had high anxiety at late pregnancy. Sleep disturbance was high, with nearly 60% of women scoring above the PSQI cut-score at both mid- and late-pregnancy. Twenty-eight percent of women at mid-pregnancy (T1) had CES-D scored at or above the cut-score ($\geq$16), suggesting risk for depression. As pregnancy progressed, only 7% of women scored above the cut-score for depressive risk at T2; however this decrease may have been influenced by attrition of subjects from T1 to T2. An evaluation of differences in psychological status by household income (above and below $60,000) revealed that women with household

incomes less than $60,000 reported significantly greater levels of depression (CES-D) and lower social support. These findings demonstrate that women with lower income have greater risk for psychological morbidity during pregnancy.

Childhood Adversity

To date few studies have evaluated the influence of maternal childhood adversity on maternal prenatal mental health and birth outcomes, as accomplished in this study. Women enrolled in this study experienced childhood trauma in the low to moderate range of intensity, and of the five CTQ subscales, the most frequent forms of adversity were emotional abuse and neglect and physical neglect. Frequency of adversity for each subscale ranged from 15% to 23%.

Key findings demonstrated that at mid-pregnancy and late-pregnancy, higher levels of maternal childhood adversity (CTQ) were associated with higher levels of perceived stress (PSS), depression (EDS and CES-D), anxiety (STAI-State), and lower social support (SPA). With respect to CTQ subscales, *emotional neglect* was positively related to perceived stress (PSS T1), depression (CES-D T1 and T2), anxiety (STAI T1), and mood disorder (POMS-65 T2), and negatively related to social support (SPA T1 and T2). *Emotional abuse* was positively related to perceived stress (PSS T1), depression (CES-D T1and T2), and anxiety (STAI T1), and negatively related to social support (T2). Additionally, *physical neglect* was positively related to perceived stress (PSS T1), depression (CES-D T1and T2), anxiety (STAI T1), and mood disorder (POMS-65 T2), and negatively related to social support (SPA T1 and T2). *Physical abuse* was positively related to perceived stress (PSS T1), depression (CES-D T1and T2), and mood

disturbance (POMS-65–total score T2), and negatively related to social support (SPA T1 and T2). Mean differences in depression (EDS) were observed in women above the normative mean cut-score for the CTQ when compared to women below the cut-score.

Distress Composite Score

Unlike prior studies, which measured only stress perception or mood, in the present study a Distress Composite Score was derived to provide a *more comprehensive and integrated index of maternal stress perception, which included the emotional/behavioral response to that perception.* Findings revealed that women exposed to greater levels of childhood adversity had higher Distress Composite Scores. Furthermore, women who had higher Distress Composite Scores and higher levels of childhood adversity delivered infants with lower birthweight and lower gestational age.

Sleep Quality

Sleep disturbance was found to be an important predictor of worse psychological well-being during pregnancy. In the present sample, over 50% of women reported poor and interrupted sleep at mid- and at late-pregnancy; while increased sleep disturbance (global PSQI) was associated with greater perceived stress, depressive risk (both EDS and CES-D), anxiety (STAI), and mood disturbance—but with lower social support (SPA). Moreover, poor sleep during late pregnancy was associated with lower birthweight and earlier gestational age.

Social Support

Social support emerged as an important moderator of maternal mental health and infant outcomes. Women with greater exposure to childhood adversity reported having

lower social support at both mid-pregnancy and late-pregnancy. Moreover, social support moderated the association between childhood adversity and birthweight. Those results revealed that women who experienced greater childhood adversity, together with less social support during their pregnancy, delivered infants with lower birthweight; in contrast, this effect was attenuated in women who reported higher levels of social support. In a similar manner social support also attenuated the association between childhood adversity and gestational age. These findings are significant as they suggest social support buffers the negative impact of maternal childhood adversity on infant birthweight. As such, these findings support the assessment of a women's level of social support as part of her prenatal care, as well as the incorporation of approaches aimed at fostering meaningful social relationships in pregnant women.

Proinflammatory Cytokines

It is well-established that proinflammatory cytokines play a role in embryo implantation and timing of delivery, and levels of these cytokines can be influenced by maternal psychological distress (Challis et al., 2009). A key finding of this study was that childhood adversity moderated the association between IL-6 and infant outcomes. That is, women with a history of greater childhood adversity who had higher circulating levels of IL 6 in late-pregnancy (T2) delivered lower birthweight infants and infants with earlier gestational age. Furthermore, an analysis of the five subscales within the CTQ revealed that physical abuse was positively correlated with circulating levels of IL-6 at T2 (controlling for pre-pregnancy BMI).

Hair Cortisol

Hair cortisol was measured in this study as an index of total HPA activation over the preceding three months. The findings revealed that hair cortisol was not correlated with key psychosocial variables or CTQ subscales at mid-pregnancy or late-pregnancy. These findings are inconsistent with earlier work showing that higher levels of hair cortisol correlated with increased psychological distress during pregnancy (Karlen, Frostell, Theodorsson, Faresjo, & Ludvigsson, 2013) (Kalra, Einarson, Karaskov, Van Uum, & Koren, 2007). The lack of finding such a relationship in the present study may be due to the small sample size. Furthermore, it is important to note that the psychometric instruments did not ask women to assess each psychological construct over the past three months (as hair cortisol does); and this difference in time domain may have impacted the study findings. However, results from the present study revealed that maternal childhood adversity moderated the association between hair cortisol and birthweight; such that women evaluated during the third trimester who were exposed to greater childhood adversity and higher concentrations of hair cortisol had infants with greater birthweight. Similarly, maternal childhood adversity moderated the association between hair cortisol and gestational age late in pregnancy; such that women with greater childhood adversity and higher hair cortisol delivered infants with greater gestational age.

The discussion of key findings is organized under the following topics: Maternal Childhood Adversity and Psychological Morbidity; Stress, Inflammation and Infant Outcomes; Other Factors Related to Inflammation and Birth Outcomes; Stress Perception and Distress Composite Score; Maternal Depression and Inflammation; Sleep

Disturbance During Pregnancy; Social Support During Pregnancy; Hair Cortisol and Stress Perception; Hair Cortisol and Infant Outcomes; Limitations; Conclusions and Implications. Of note, findings related to levels of proinflammatory cytokines and neonatal outcomes are integrated throughout.

Discussion of Key Findings

Maternal Depressive Symptoms and Inflammation

A major objective of this study was to evaluate the impact of maternal childhood adversity on psychological well-being of pregnant women, infant birthweight, and gestational age. Childhood abuse and/or maltreatment are a major public health issues, as they are associated with later life risky behaviors as well as adult mental and physical health problems (Molnar, Buka, & Kessler, 2001; Seng, Sperlich, & Low, 2008). A surprising number of women experience some form of childhood abuse or maltreatment. For example, findings from a community-based sample (Memphis, Tennessee; N=947) of women revealed that as many as 30% of women experienced enduring childhood abuse, neglect, or hardship (Scher, Forde, McQuaid, & Stein, 2004). The most common forms of trauma were physical abuse, physical neglect, and emotional abuse. A more recent population-based epidemiologic study (Boston Area Community Health Survey; N=3,201) revealed the prevalence of childhood physical, emotional, and sexual abuse in a diverse community-dwelling sample of women to be 21%, 19%, and 26%, respectively (Chiu et al., 2013). Further, such adversity is even more common in women raised under conditions of socioeconomic disadvantage (Holzman et al., 2006).

Early life adversity is known to have long-lasting effects on adult stress reactivity and mental health, particularly risk for depression (Molnar et al., 2001). Yet few studies have evaluated the impact of early life adversity on maternal psycho-neuro-immune profile and infant outcomes, as in the present investigation. For this study, maternal childhood adversity was measured retrospectively using the Childhood Trauma Questionnaire (CTQ). The CTQ assesses childhood trauma in five domains: emotional neglect and abuse, physical neglect and abuse, and sexual abuse. For women in the present sample, the intensity of childhood trauma was in the low to moderate range; and frequency for each of the subscales ranged from 15-23%.

Findings from this study revealed that women exposed to higher levels of childhood adversity had significantly higher levels of perceived stress and anxiety, as well as increased depressive risk (CES-D and EDS). There is a limited literature linking exposure to childhood adversity with poorer maternal mental health during pregnancy (Lang, Rodgers, & Lebeck, 2006). Of note, Rich-Edwards and colleagues reported a 26% higher risk for depression during pregnancy in women exposed to abuse during childhood or adolescence. This larger risk was observed in two economic and ethnic distinct cohorts (Rich-Edwards et al., 2011), suggesting that childhood adversity impacts women independent of income and ethnicity. Yet others do find that the association between childhood adversity and prenatal depression is especially strong among disadvantaged women, possibly contributing to health disparities in birth outcomes (Holzman et al., 2006). In the present study, an evaluation of CTQ scores based on income revealed no differences, likely reflecting the fact that most participants had

household incomes above the federal poverty line. Furthermore, an evaluation of CTQ scores and subscales of the CTQ revealed no mean differences based on race (White n=21, non-White n=32); yet, the sample size is small and evaluation of racial differences in CTQ is underpowered.

Overall the results of the present study add to growing evidence linking childhood adversity to poor mental health during pregnancy. Most importantly, the findings demonstrate a significant correlation between childhood adversity and depressive symptoms; that is, higher scores on the CTQ were significantly related to higher scores on the CES-D T1 and T2 (general depressive risk at both mid and late-pregnancy), as well as the EDS T1 (pregnancy depressive risk at mid-pregnancy). Additionally, higher CTQ scores were significantly related to higher scores on PSS T1 (perceived stress at mid-pregnancy) and STAI T1 (anxiety at mid-pregnancy). Others have shown that greater maternal depressive symptoms are related to lower birthweight (Grote et al., 2010) and to poor neurobehavioral outcomes (Field, 2011). *Thus, finding a positive relationship between childhood adversity and depressive symptoms is not inconsequential, but suggests that childhood adversity is an important vulnerability factor for prenatal depressive risk.*

Lastly, women in the present study who reported greater exposure to childhood adversity also reported less social support during their pregnancy. Given that this data is correlative, it is impossible to determine if these two variables are causally related. Yet, these results suggest that pregnant women who have greater childhood adversity may be in need of more supportive relationships. Social support reduces maternal depressive

symptoms (Razurel & Kaiser, 2015) and levels of psychological distress (Iranzad, Bani, Hasanpour, Mohammadalizadeh, & Mirghafourvand, 2014; S., Hasanpour, S. et al, 2014). Given that childhood adversity has been linked to increased lifetime risk of depression in non-pregnant women (Gilman, Kawachi, Fitzmaurice, & Buka, 2003) (Gilman, Kawachi, Garrett, & Buka, 2002), social support may provide psychological benefit to pregnant women exposed to childhood adversity (Gilman et al., 2003; Gilman et al., 2002).

Stress, Inflammation, and Infant Outcomes

Pregnancy is characterized by defined fluctuations in the circulating levels of immune-derived inflammatory molecules (Challis et al., 2009), which influence the timing of gestation and fetal growth (Challis et al., 2009). In normal pregnancy the first and third trimesters are predominately characterized by a proinflammatory milieu, whereas the second trimester is dominated by an anti-inflammatory milieu (Mor, Cardenas, Abrahams, & Guller, 2011). As demonstrated in prior research, increased maternal distress perception during pregnancy can lead to elevations in proinflammatory cytokines, particularly IL-6 and TNF-alpha (Coussons-Read et al., 2007; Coussons-Read et al., 2005). Disruption in the balance of pro- and anti-inflammatory cytokines is also implicated in adverse birth outcomes, such as intrauterine growth restriction (J. R. Challis et al., 2009) and onset of premature labor and parturition (Romero et al., 1989; Hillier et al., 1993). Others (Georgiou et al., 2011) have shown that of 21 cytokines/chemokines measured at 7-10 weeks gestation, increases in proinflammatory cytokines (interferon-γ, interleukin [IL]-2, -7, -12) and decreases in anti-inflammatory cytokines (IL-1 receptor

antagonist, -4, -10, -13) were associated with small for gestational age infants (Andersgaard et al.). In addition, eotaxin and macrophage inflammatory protein-1α were higher; and monocyte chemoattractant protein-1 and IL-8 were lower (Georgiou et al., 2011). Others demonstrated a significant correlation between elevated inflammatory markers in cord blood from SGA infants, suggesting an inflammatory process in intrauterine growth restriction (Lausten-Thomsen, Olsen, Greisen, & Schimiegelow, 2014). A more recent integrated review concluded that the most consistent finding within this literature is that increased levels of proinflammatory cytokines (measured in blood), especially IL-6, IL-1beta, and TNF-alpha, are associated with preterm birth. However, those authors note that there are relatively few studies and results are inconsistent (Lyon et al., 2010).

The findings from the present study did not reveal any relationships between proinflammatory cytokines (IL-6 and TNF-alpha) and infant birthweight or gestational age (when applying the Bonferroni correction). It is likely that the small sample size and low number of low birth weight and preterm births reduced the likelihood of finding such a relationship. Nevertheless, there remains a need for further research to determine if and how proinflammatory cytokines during pregnancy contribute to poor infant outcomes. Furthermore, as discussed below, maternal exposure to childhood adversity may interact with the proinflammatory environment of pregnancy to influence birth outcomes.

Maternal Childhood Adversity, Inflammation, and Infant Outcomes

Low birthweight (LBW) is a significant public health problem, as LBW is not only associated with complications in the neonatal period, but is also linked to worse

health for such infants over their life span (Barker, 2002; Rich-Edwards et al., 2011; Rich-Edwards et al., 2005). Importantly, a series of investigations find LBW to be linked to major adult chronic disease, such as cardiovascular disease, obesity, and diabetes (Oken & M.W., 2003; Whincup et al., 2008). These observations have given rise to the fetal origins of disease theory; also, referred to as the Developmental Origins of Health and Disease (DOHaD) theory (Barker, 2002). Investigations aimed at understanding risk for infant LBW are now extending beyond the narrow window of pregnancy to include the examination of risk antecedent to a women's pregnancy, including experience of early life adversity. Such investigations can inform the development of preventive strategies delivered prior to conception (i.e., pre-conception care). In this respect, "prenatal care" should be expanded to incorporate a lifespan approach and to include intervention strategies aimed at addressing early life maternal psychosocial conditions (Gavin, Thompson, Rue, & Guo, 2012).

At this time, there is a limited literature describing linkages between maternal early life adversity and increased risk for infant LBW (Gavin, Hill, Hawkins, & Maas, 2011; Gavin et al., 2012; Plant, Barker, Waters, Pawlby, & Pariante, 2012). However, a few prospective studies find maternal low SES in childhood and exposure to maternal childhood hardship to be associated with delivery of LBW infants (Atstone, Misra, & Lynch, 2007; Gisselmann, 2006; Atstone et al., 2007). Recent findings from a study that evaluated California birth records from 153,762 live singleton infants born to adolescent mothers concluded that maltreatment history was associated with infant LBW (<2500 gm) (Putnam-Hornstein, Cederbaum, King, Eastman, & Trickett, 2015). [Of note,

maternal maltreatment history was determined based on child protection data from public records.]

Currently, there is little understanding of the biological mechinisms that link maternal early life adversity to poor infant outcomes and this remains an area of evolving investigation. *Findings from the present study demonstrate that childhood adversity and IL-6 interact with influence infant birthweight and gestational age, which has not been previously reported.* That is, women with a history of greater childhood adversity who also had higher circulating levels of IL 6 in late-pregnancy delivered infants with lower birthweight and earlier gestational ages. Probing this interaction using the Johnson-Neyman technique revealed that women who scored greater than 58.1 on the CTQ were at significantly greater risk to have lower birthweight babies if they also had higher levels of plasma IL-6. Similarly, the findings of the present study revealed a significant interaction between exposure to childhood adversity and plasma IL-6 levels. That is, women who experienced higher levels of childhood adversity and who had higher levels of plasma IL-6 delivered infants with earlier gestational age. Probing this interaction using the Johnson-Neyman technique revealed that women who scored greater than 51.1 on the Childhood Trauma Questionnaire (CTQ) were at significantly greater risk to deliver lower gestational age infants if they also had higher levels of IL-6. Such findings regarding the interaction between maternal childhood adversity and IL-6 to influence infant birthweight and gestational age have not been previously reported.

It is possible that exposure to childhood adversity modifies the inflammatory response to stressful life events experienced during adulthood. Early life stress alters

neurobiological processes of the brain during development (including childhood), a time when the brain is more plastic and thus more susceptible to adverse environmental stimuli; and these changes persist over the lifespan (Danese and McEwen, 2011; Heim et al., 2010; Nemeroff, 2004). Non-pregnant adults exposed to childhood adversity manifest greater emotional responsiveness to stressors (McLaughlin et al., 2010a), as well as an increased autonomic nervous system and dysregulated HPA stress response (Heim et al., 2008). Prior work also demonstrates that early life adversity predisposes to a proinflammatory phenotype. For example, those who experienced lower childhood socioeconomic status, and likely more adversity, exhibited higher circulating levels of IL-6 (Carroll et al., 2011). Findings from a longitudinal study demonstrated childhood maltreatment predicted risk for low-grade inflammation during adulthood, independent of adult and child socioeconomic status and health behaviors (Danese et al., 2007). In response to acute stress, exposure to childhood adversity resulted in an exaggerated proinflammatory response. Healthy adults who experienced childhood maltreatment mounted a greater plasma IL-6 response to an acute laboratory social evaluative stress test (Trier Social Stress Test–TSST), compared to those without a history of childhood maltreatment (Carpenter et al., 2010). Consistent with this finding, older adults exposed to childhood adversity were found to have greater circulating IL-6 and TNF-alpha levels when experiencing the naturalistic and chronic stress associated with caregiving for others with dementia (Kiecolt-Glaser et al., 2010). Other evidence showed that this proinflammatory phenotype linked to early life adversity emerged during young adulthood, as peripheral blood mononuclear cells derived from young women raised in a

harsh family climate produced more IL-6 in response to *in vitro* challenge with lipopolysaccharide and in response to real life psychological stressors (Miller & Chen, 2010). Moreover, individuals with a history of adversity during childhood are at higher risk for depression and mood disorders later in life, especially when under acute stressful situations (Chen et al., 2010b; Heim et al., 2010; Hill et al., 2000; Nemeroff, 2004), and pregnancy can be associated with multiple life challenges and emotional upheaval. Leigh and colleagues found that women with low income and history of abuse had greater risk for antenatal depression (Leigh & Milgrom, 2008). In line with this, the present findings revealed a positive correlation between maternal childhood adversity and increased depressive symptoms.

In summary, the results from the present study support the concept that childhood adversity interacts with elevated levels of proinflammatory cytokines to alter timing of birth and fetal growth. *These results add to the existing body of evidence in non-pregnant individuals that suggests childhood adversity engenders an adult proinflammatory phenotype, in turn suggesting an extension of this concept to risk of lower birthweight and earlier gestational age.* To the author's knowledge, this has never been reported previously.

Other Factors Related to Inflammation and Birth Outcomes

Other factors may also play a role in modulating levels of maternal proinflammatory cytokines. For example, elevations in maternal inflammatory markers may be associated with greater BMI and this may also contribute to altered fetal growth. Findings from the present study revealed that higher pre-pregnancy BMI (n=60, r=.573,

p<.000, n=46, r=.546, p<.000), as well as higher mid-pregnancy BMI (n=60, r=.572, p<.000, n=46, r=.573, p<.000), was significantly associated with higher levels of circulating IL-6 at both T1 (second trimester) and T2 (third trimester). Of note, the present study relied upon maternal self-report of pre-pregnancy BMI, which may not be accurate, but was the only possible way to access BMI in the women participating in this study. Interestingly, a recent study (Aye et al., 2014) showed that maternal BMI was not only associated with elevated maternal proinflammatory cytokines but also activation of placental inflammatory pathways; although no changes in fetal circulating inflammatory molecules were observed. These authors suggest that elevated maternal BMI may influence fetal growth by altering placental function. Although beyond the scope of this dissertation research, findings from several other studies suggest that greater risk of small-for-gestational age (Andersgaard et al.) infants (Andersgaard et al.) is associated with common anti-inflammatory cytokine polymorphisms, and this may vary with race (Engel et al., 2005). More recent data confirms the existence of gene-level associations between IL-6 and SGA among African American women (Harmon et al., 2014). These findings demonstrate that both environmental and genetic risk factors can modulate inflammatory risk for SGA.

In addition to inflammatory processes, health behaviors may also influence the relationship between childhood adversity and birth outcomes. For example (Gavin et al., 2012), using structural equation modeling to investigate paths whereby childhood adversity influenced infant birthweight, poor maternal health behaviors during adolesence (substance abuse and cigarette use) were found to partially mediate the relationship

between maternal SES and infant birthweight, indicating that maternal depressive symptoms and adult SES partially mediated this relationship as well. Additionally, findings from that study showed maternal substance abuse and prenatal cigarette use partially mediated the relationship between maternal childhood maltreatment and offspring birthweight; and that maternal adolescent depressive symptoms and adult SES also partially mediated this relationship. Women in the current sample reported low levels of cigarette use (3%) and alcohol use (6%), so these risk factors likely play little role in study findings.

Stress Perception and Distress Composite Score

Perceived stress was measured at both mid and late pregnancy using the Perceived Stress Scale (PSS). This is a general tool in which respondents rate how manageable events in their life were perceived over the past month (Cohen, Kamarck, & Mermelstein). In this sample of pregnant women, 63% and 52% reported levels of perceived stress above the population norm of 13 during their second and third trimester of pregnancy, respectively; and mean levels were above the reported norms for healthy non-pregnant women in this age group (Sheldon Cohen & Janicki-Deverts, 2012). Further, mean perceived stress scores were higher in women who had experienced greater levels of childhood adversity, with total and subscale CTQ scores positively correlating with perceived stress at mid- and late-pregnancy. Although correlative, these findings suggest that women who were exposed to greater adversity during their childhood are more likely to perceive events in their life as less manageable, escalating risk for mood disturbance during their pregnancy.

To provide a more comprehensive and multifaceted index that captures both stress perception and emotions/mood across pregnancy, a Distress Composite Score was derived based on scores from instruments measuring perceived stress (PSS), depressive risk (CESD), anxiety (STAI), mood disorder (POMS-65), and sleep quality (PSQI). Factor analysis revealed these measures comprised a single factor at both mid-pregnancy and late-pregnancy. [Of note, the weakest variable in the model was sleep quality; however, it was maintained in the final model.] It was anticipated that the use of a composite score would provide an index that more fully captured the multiple facets that encompass the psychological stress response; that is, inclusion of the *perception* of stress, as well as the emotional and behavioral *response* to stress perception. This approach, in fact, did yield valuable insight as to the interactions among maternal childhood adversity, distress, mood, and infant birth outcomes; which were not observed when solely using the PSS. Specifically, findings from evaluation of regression models revealed a significant interaction between the Distress Composite Score at T2 (late pregnancy) and childhood adversity; such that women who had higher Distress Composite Scores and higher levels of childhood adversity delivered lower birthweight infants. Additional probing of this interaction (Johnson-Neyman post hoc analyses) revealed that for women who scored greater than 56.3 on the Childhood Trauma Questionnaire (approximately 10% of the present sample), the negative relationship between the Distress Composite Score and birthweight was significant. In a similar manner, regression analysis revealed a significant interaction between the Distress Composite Score at T2 and childhood adversity, such that women who had higher Distress Composite Scores and higher levels

of childhood adversity delivered infants with lower gestational age. Probing this interaction (i.e., Johnson-Neyman post hoc analyses) revealed that for women who scored greater than 49.4 on the Childhood Trauma Questionnaire (approximately 13% of the present sample), the negative relationship between Distress Composite Score and birthweight was significant.

Together these findings suggest that women with exposure to higher levels of childhood adversity together with higher Distress Composite Scores delivered infants with lower birthweight and earlier gestational age (i.e., earlier delivery). These findings, however, are limited in that this was a convenience sample of low-risk pregnant women, who overall had a low incidence of preterm and low birth weight infants (based on clinical definitions), compared to high risk pregnant women. As noted earlier, the national rate of premature delivery is 11.4%, while low birthweight delivery accounts for 8.0% of births (Martin et al., 2015). Premature delivery in the present study was slightly lower than national average (9%), but consistent with the incidence of low birthweight delivery (8.6%). As well, preterm infants vary by race and ethnicity, with higher rates for African American women (16.8%) and Hispanic women (12.1%), compared to White women (10.5%) (March of Dimes, 2015). Thus, future studies should enroll high-risk pregnant women to gain further insight as to the role of exposure to maternal psychological stressors and early life adversity on infant outcomes.

Nevertheless, the above results are consistent with a growing body of evidence which documents that maternal prenatal daily hassles, depression, anxiety, and the experience of negative life events during pregnancy, result in earlier delivery and lower

birthweight infants (Talge, 2007). Notably, a recent meta-analysis (Littleton, Bye, Buck, & Amacker, 2010 & Amacker, 2010) of 35 studies (N=31,323 women) demonstrated that exposure to psychosocial stressors during pregnancy was significantly associated with risk for low birthweight; but this association, although significant, was very small. The authors concluded that other lifestyle variables and/or risk factors (i.e., vulnerability factors) need to be considered in combination with measures of psychosocial distress to more fully address the role of prenatal distress on prematurity and birthweight. As the results of the present study suggest, maternal childhood adversity represents a potentially important prenatal (and pre-conceptual) vulnerability factor for poor neonatal outcomes.

Maternal Depressive Symptoms and Inflammation

Depression during the prenatal period has major consequences for mothers and their children, including greater risk for prematurity, low infant birthweight (Grote et al., 2010), and poor neurobehavioral outcomes (Field, 2011). However, the biological pathways mediating risk for depressive disorders in the perinatal period remains to be clarified. Many potential mechanisms are currently investigated and these include genetic risk (Mahon et al., 2009), dysregulation of the HPA axis (Brummelte & Galea, 2010; Groer & Morgan, 2007), sensitivity to changes in steroid hormone levels (Brummelte & Galea, 2010) (Bloch et al., 2000) and altered levels of proinflammatory cytokines subsequent to sleep disruption (Okun & Coussons-Read, 2007; Okun et al., 2007).

Women enrolled in this study reported mean CES-D scores of 12.9 and 7.8 for T1 and T2, respectively. At T1 28% of the women scored above the established CES-D score ($\geq$16), suggesting risk for depression; while only 7% scored above this score at T2,

suggesting that depressive risk numerically decreased with progression of pregnancy. However, it is also possible that the women who did not complete the T2 time-point (due to attrition) may have been the women with greater depressive risk; hence, contributing to lower T2 CES-D scores. Interestingly, only 10% and 7% of the women scored above the cut-score on the Edinburgh Depression Scale ($\geq$13), for T1 and T2, respectively. CES-D is a measure of general depressive risk, while EDS is more specific to signs and symptoms of depressive risk during pregnancy and the post-partum period. It is possible that rates of depressive risk may be higher on the CES-D when compared to the EDS because the CES-D includes items that address fatigue, sleep, and other vegetative symptoms of depression that overlap with normal "symptoms" of pregnancy.

Contrary to what was hypothesized, this study did not find any relationship between both proinflammatory cytokines (IL-6 or TNF-alpha) and depressive symptoms (when applying the Bonferroni correction). These findings do not support the inflammatory theory of depression, which posits that increases in circulating levels of proinflammatory cytokines engender symptoms of depression; however, the evidence in humans for this theory is largely based on studies of individuals with major depressive disorder (Raison, Capuron, & Miller, 2006). For example, a recent meta-analysis found that compared to control subjects, individuals with major depression had significantly higher levels of IL-6 and TNF-α; while associations with other cytokines were not significant (Dowlati et al., 2010). The exclusion of women with major depressive disorder likely limited the finding of a relationship between proinflammatory cytokines and depressive symptoms in the present study.

Furthermore, there are mixed findings in the literature as to whether there is any relationship between proinflammatory cytokines and depressive symptoms in pregnant and postpartum women; and this evidence was recently reviewed (Osborne & Monk, 2013). One key study evaluated pregnant women during the late first and early second trimester and found depressive symptoms (CES-D) were associated with increased circulating levels of IL-6 and marginally increased levels of TNF-alpha, while controlling for pre-pregnancy BMI (Christian et al., 2009). In that study nearly 60% of participants were low-income African American women, with half scoring at or above the clinical cut-off score for depressive risk using the CES-D. Others also report depressive symptoms (CES-D) to be correlated with higher circulating levels of IL-6 and IL-1 beta, but not TNF-alpha, during the second trimester of pregnancy (Cassidy-Bushrow et al., 2012). The sample for that study included a sizable number of African American women with varied SES backgrounds, and almost 40% of this sample reported CES-D scores suggestive of depressive risk. Additionally, 70% of the samples were overweight or obese (based on pre-pregnancy weight), and BMI moderated the association between depressive symptoms and IL-6. Leaner women with depressive symptoms had higher circulating levels of IL-6, but the relationship between IL-6 and depressive symptoms lessened as BMI increased; these results emphasize the potential contribution of pre-pregnancy BMI in the linkages between inflammation and depression during pregnancy. For the present study, pre-pregnancy BMI was controlled in order to account for any potential influence of adiposity on circulating levels of IL-6 and TNF-alpha.

In contrast to the above studies, Blackmore et al., 2014 reported no relationship between depressive mood and IL-6 in a sample of low income women evaluated at 18 and 32 weeks of gestation (Blackmore Robinson, Groth, Gilchrist, O'Connor, & Moynihan, 2014); that study used the Edinburgh Prenatal Depression (EDS) scale. This finding is consistent with the results of the present study. However, even though the study by Blackmore et al. (2014) had many strong features, including large sample size, multiple assessment times, and within-participant comparisons, it did not include high risk women with diverse socioeconomic backgrounds for whom the inflammation-depression link may be most clinically pertinent and evident. As well, the present study did not enroll a substantial number of high-risk women with diverse socioeconomic background. In another study, White women evaluated during the second trimester exhibited an inverse association between depressed mood and three cytokines (IL-1 beta, TNF-alpha, and IL-7) (Shelton, Schminkey, & Groer, 2015). That study was limited by the use of the non-specific depression/dejection subscale of the Profile of Moods State (POMS) to measure depressive mood; and furthermore, the sample included few women reporting depressive symptoms, suggesting a possible 'floor effect.' Likewise, no association was found in this study between scores on the POMS subscale and proinflammatory cytokine levels.

Another potential caveat is that the majority of studies investigating the relationship between proinflammatory cytokines and perinatal depression measured resting levels of circulating proinflammatory cytokines. As pointed out by others, greater insight may be obtained by evaluating the proinflammatory response to a stress

challenge, which will induce greater variability among subjects and increase the possibility that individual differences will be measurable (Christian, 2014). One such study evaluated the inflammatory response to influenza vaccine challenge in a sample of pregnant women, assessed before and one week after the vaccine. Findings revealed that women scoring in the highest tertile for depressive symptoms (CES-D) had significantly higher levels of the cytokine macrophage migration inhibitory factor (MIF) at the post-vaccine time point. MIF is a proinflammatory molecule and has been associated with premature birth (Pearce et al., 2008).

There are many factors that contribute to mixed results and limit comparison across studies, including: variation in the timing of maternal evaluation, socio-demographics of the sample, control of confounders, instruments used to measure depressive mood, range of depressive scores, and variation in inflammatory outcomes measured. Osborn and Monk emphasize the need for a more "nuanced" approach to be able to discern linkages between proinflammatory cytokines and maternal depressive symptoms (Osborne & Monk, 2013), and recommend that future studies enroll women who have greater psychosocial risk and more diverse socio-demographic backgrounds. Importantly, there is a need for future investigations to enroll high-risk women, especially African American women, who are known to mount a greater inflammatory response to stressors than other racial groups (Carroll et al., 2009; Gruenewald, Cohen, Matthews, Tracy, & Seeman, 2009; Gruenewald et al., 2012). Evidence suggests that African American women have cytokine genotypes that up-regulate inflammation (Ness, Haggerty, Harger, & Ferrell, 2004), and this may be linked to worse pregnancy outcomes

(Dominguez, Dunkel Schetter, Mancuso, & Hobel, 2005). Further, stress-induced inflammatory responses are more robust among pregnant African American women compared to pregnant White women (Christian, Iams, Porter, & Leblebicioglu, 2013). In the present study, the small number of African American women enrolled did not allow an evaluation of the interaction between African American race and inflammation on depressive risk.

A deeper understanding of the depression-inflammation link will also be gained by including measurement of resilience factors, such as social support, spirituality, and the meaning women associate with being pregnant and parenting. *Social support was found in this study to buffer the negative impact of childhood adversity* and is discussed below. It is also important that valid measures of depressive symptoms are not confounded by assessment of somatic symptoms that occur in normal pregnancy, and may require new instrument development. Although beyond the scope of this study, cytokines measured should include both pro- and anti-inflammatory cytokines, as well as assessment at multiple time periods to more carefully evaluate shifts in cytokines across pregnancy. Finally, depression during specific trimesters of pregnancy and the postpartum period needs to be differentiated, as each trimester of pregnancy and the postpartum period are distinct physiologic states characterized by significant psychological adaptation, as well as unique adaptations of the immune system that may result in dynamic fluxes in the proinflammatory milieu.

Depressive symptoms, along with anxiety and stressors during pregnancy, may affect infant birth outcomes. A systematic review of 39 studies found significant but

complex paths of interactions between depression, anxiety and stressors, and risk factors for preterm birth. Of note, pregnancy distress was associated with spontaneous but not with medically indicated preterm births (Staneva, Boggossian, Pritchard, & Wittkowski, 2015). This is consistent with findings from the present study in which depressive symptoms at late pregnancy were significantly related to lower gestational age (not preterm birth per se); however these findings were no longer apparent once a Bonferroni correction was applied to reduce chance for Type 1 error. Nevertheless, these results suggest women who experience greater depressive symptoms are more likely to deliver an infant with lower gestational age; perhaps increasing the risk for premature delivery. *These findings imply that provision of appropriate support to women experiencing depressive symptoms may improve outcomes for both mothers and infants.*

Sleep Disturbance during Pregnancy

During pregnancy and the postpartum period, women are at higher risk for sleep disturbance because of pregnancy-related physical alterations and the demands of caring for a newborn. During the first trimester of a healthy pregnancy, women have an increase in total sleep time and experience high levels of daytime sleepiness, implying that sleep needs are increased in early pregnancy (Hedman, Pohjasvaara, Tolonen, Suhonen-Malm, & Myllyla, 2002); whereas during the third trimester women report a decrease in sleep time and an increase in nocturnal awakenings (Hertz et al., 1992). Evidence demonstrates that sleep disturbance has high potential to moderate and possibly compound the adverse effects of prenatal stressors and negative mood (Field, Diego, Hernandez-Reif, Figueiredo, Deeds, Ascencio, Schanberg, & Kuhn, 2010; O'Connor et

al., 2007), increasing the risk for adverse maternal and fetal outcomes. Thus, in this study maternal sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a general sleep quality index used extensively in healthy and ill populations (Okun & Coussons-Read; Okun et al.; Okun, Luther, Wisniewski, & Wisner; Okun, Roberts, Marsland, & Hall; Okun, Roberts, Marsland, & Hall; Okun, Schetter, & Glynn). More recently the PSQI was demonstrated to be a reliable and valid tool for use during pregnancy and postpartum (Okun, Hanusa et al., 2009; Okun et al., 2013). In the present study over half of the sample reported poor and interrupted sleep at mid- and at late-pregnancy. In addition, during mid-pregnancy, increased sleep disturbance (global PSQI) was significantly related to greater perceived stress, depressive risk (both EDS and CESD), anxiety (STAI), and mood disturbance. These relationships remained significant during late pregnancy, except for anxiety. These findings are consistent with results of a recent longitudinal study demonstrating distinct trajectories of sleep quality (using the PSQI) in women from pregnancy through the postpartum period. Finding from that study revealed that women who reported the highest levels of poor sleep during pregnancy also had the highest levels of anxiety and depressive symptoms in early pregnancy and the lowest levels of social support. Further, women with the worst subjective sleep quality during pregnancy were also the most likely to experience high symptoms of depression in the postpartum period (Tomfohr, Buliga, Letourneau, Campbell, & Giesbrecht, 2015). Together these findings indicate that sleep can be an important predictor of worse psychological well-being during pregnancy and the postpartum period, and suggest health care providers should assess both duration and quality of sleep in women during the

perinatal period. Findings of previous studies suggest sleep disturbance may exacerbate risk for maternal depression (Chang, Pien, Duntley, & Macones, 2010). As such, *these findings identify maternal childhood adversity as a vulnerability factor that may predispose to greater sleep disturbance and risk for perinatal depression.* Of note, in this study sleep disturbance was positively related to greater depressive risk. Okun, Kiewra, Luther, Wisniewski, and Wisner (2011), identify pregnant women with poor sleep are greater in women with depression as compared to women without depression. This is an important finding given that poor sleep during pregnancy and the postpartum period is linked to postpartum depression (Chang et al., 2010) and poor maternal care behaviors endanger infant/child development (Murray, Cooper, & Fearon, 2014).

In addition, sleep deprivation during pregnancy may elevate risk for preterm delivery, and systematic inflammation has been hypothesized to underlie this association (Chang et al., 2010). Findings from this study show that poor sleep during late pregnancy was not related to lower birthweight and earlier gestational age once a Bonferroni correction applied. Also, no associations between sleep quality and the proinflammatory cytokines measured (IL-6 and TNF-alpha) were found. Prior research linking sleep disturbance, proinflammatory cytokines, and poor birth outcomes is mixed. Some investigators report that third trimester sleep disruption is associated with increased levels of the pro-inflammatory cytokine, IL-6 (Okun & Coussons-Read, 2007; Okun et al., 2007). In contrast, others report no effects of third trimester sleep disruption on IL-6 levels (Okun et al., 2007). This inconsistency across studies is likely attributed to varying measures of sleep, variation in the time during pregnancy when sleep is assessed,

small and often non-representative samples, and lack of control for covariates—especially BMI (Chang et al., 2010). Further research, especially longitudinal studies, is needed to clarify the contribution of biological mechanisms as to how poor sleep jeopardizes maternal and neonatal health. The findings from this study, however, do suggest that the development and testing of behavioral and/or educational interventions designed to provide information, strategies, and support to promote maternal and newborn sleep can benefit maternal health and infant development. This direction is consistent with findings from a recent study which showed that greater maternal napping frequency was associated with better cognitive development of the infant (Ronzio, Huntley, & Monaghan, 2013).

Social Support during Pregnancy

Findings from this study revealed that lower levels of social support were associated with higher levels of perceived stress, depressive symptoms (EDS and CES-D), and anxiety at both mid-pregnancy and late-pregnancy. Prior results from a meta-analysis reveal that low levels of social support, along with higher levels of emotional stressors, during pregnancy are strong predictors of postpartum depression (Robertson, Grace, Walllington, & Stewart, 2004) and these findings were confirmed in a recent prospective study (Morikawa et al., 2015). As well, others recently reported that maternal satisfaction with social support at late pregnancy and early postpartum was associated with lower depressive symptoms and anxiety after delivery (Razurel & Kaiser, 2015), while others identified women with low social support as experiencing greater stressors across pregnancy (Iranzad et al., 2014 S., Hasanpour et al, 2014). Thus, the present

findings add to the existing literature demonstrating that social support during pregnancy may lower stressors and protect against postpartum depression.

Few, if any studies, have evaluated the relationship between maternal early life adversity and social support during pregnancy. The findings of the present study revealed that women who reported greater exposure to childhood adversity also reported lower levels of social support; this association was observed for the total CTQ scale, as well as for CTQ subscales: emotional neglect and abuse, and physical neglect and abuse. Although correlative, these results suggest that women who have greater exposure to childhood adversity may either have inadequate social networks available to them or lack social skills needed to form meaningful social relationships. Moreover, the current findings suggest that levels of social support influence birth outcomes. Specifically, regression analysis revealed that social support moderated the association between childhood adversity and infant birthweight, such that women who experienced greater maternal childhood adversity together with lower social support during their pregnancy delivered infants with lower birthweight. In contrast, the negative impact of childhood adversity was attenuated (i.e., buffered) in women who reported higher levels of social support. In a similar manner social support attenuated the association between childhood adversity and gestational age. As such, these results suggest that the harmful effects of maternal childhood adversity on birthweight and gestational age can be reduced in women who have higher levels of social support during their pregnancy. These findings lend support to implementation of clinical approaches that engender the development of meaningful (supportive) relationships, particularly for women at risk due to high

exposure to childhood adversity. For example, prenatal classes and support groups may be designed to include not just the birth couples, but other family members and friends, as well. Ideally such support should be provided prior to or early on during pregnancy to maximize benefits. Other suggestions to increase social support during pregnancy are described in Conclusions and Implications at the end of this chapter.

Hair Cortisol and Stress Perception

During pregnancy the HPA axis undergoes remarkable change to accommodate the developing fetus (Davis & Sandman, 2010). Most striking is the increase in maternal plasma CRH (Lowry, 1993), which results from a positive feedback loop whereby cortisol stimulates CRH production by the placenta. As a result, ACTH and cortisol increase as pregnancy advances (Petraglia et al., 1996; Robinson et al., 1988). However, by term, this positive feedback loop is blunted because maternal receptors for stress hormones become down-regulated. Consequently, during late gestation environmental stress is less effective in triggering the HPA axis; thus, women become less responsive to stressors (Glenn, 2010; Glenn et al., 2001; Schuetze & Das Eiden, 2005).

Abundant evidence derived from animal models of prenatal stress demonstrate that prenatal stress exposure affects behavioral and biological development through activation of the HPA axis, and in particular its end product, the adrenal glucocorticoid hormone, cortisol (Coe et al., 2003; Maccari et al., 1996; Weinstock, 2005). Yet evidence in humans is not as definitive. It is known, however, that maternal stress response is associated with an increase in cortisol and CRH in the maternal-fetal dyad (Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando, & Bendell, 2004;

Weinstock, 2008). Others have observed that fetuses of depressed women with increased prenatal cortisol exhibit growth retardation and that these women deliver more preterm and low birthweight infants (Diego et al., 2009). Yet, there are inconsistent findings in the literature, suggesting complexity in the relationship among prenatal maternal stressors, cortisol, and child outcomes. The inconsistent findings are attributed to varied study designs, differences in defining and measuring stressors, timing of stress measurement, and sample characteristics. Likely this relationship is multifactorial with no single factor serving as the underlying mechanism (Shaikh et al., 2013).

It is also suggested that chronic or enduring stressors during pregnancy is more important than acute episodic stressors, as assessed by measuring plasma and salivary cortisol (O'Connor et al., 2002; Stott, 1973; Wadhwa, Sandman, Garite, 2001). More recently hair cortisol has been shown to be a reliable, non-invasive, retrospective measure of HPA axis activity (Russell et al., 2011); and the use of hair cortisol as an index of the HPA stress response during pregnancy has been validated (D'Anna-Hernandez, 2011). For example, hair cortisol was found to correlate with cortisol measured in salivary samples during the second and third trimesters of pregnancy; and both hair and salivary cortisol increased as gestation progressed, consistent with the known physiologic increase in cortisol over late pregnancy (D'Anna-Hernandez, 2011). Others also showed that hair cortisol levels (range = 0.06 and 0.23 nmol/g of hair) in a small sample of healthy pregnant women positively correlated with levels of perceived stress using the PSS (Kalra, Einarson, Karaskov, Uum, and Koren, 2007).

Given the potential for hair cortisol to index chronic HPA activity, hair cortisol was measured in this study during mid- and late-pregnancy as an index of HPA activity over the prior three-month time interval. In the present study, no significant relationships were found between psychological variables and hair cortisol. These findings do not support earlier work showing that higher levels of hair cortisol correlated with increased psychological stressors during pregnancy (Kalra, Einarson, Karaskov, Uum, and Koren, 2007; Karlen et al., 2013); these negative findings likely reflect the small sample size of this dissertation study.

Recent studies find maternal child sexual abuse (based on the CTQ) to be associated with increased salivary cortisol awakening response over the second and third trimesters of pregnancy (Bublitz, & Stroud, 2012; Bublitz & Stroud, 2013), implying that such abuse produces long-lasting changes of the HPA axis that manifest during pregnancy. Findings from the present study, however, did not reveal a relationship between childhood adversity and hair cortisol. Moreover, this is also in contrast to recent findings demonstrating that pregnant women with a history of childhood physical and/or sexual abuse had greater hair cortisol levels, compared to women with no history of abuse. (Schreier, Enlow, Gennings, & Wright, 2015). That study did find, however, that childhood rates of abuse and hair cortisol levels varied by race/ethnicity. Subsequent analysis of the association between childhood adversity and hair cortisol by race revealed that such associations were only significant among African American women. The low number of African American women providing hair samples in the present dissertation

study undoubtedly limited the ability to detect similar associations between maternal childhood adversity and hair cortisol in this racial group.

Hair Cortisol and Infant Outcomes

There is also evidence that hair cortisol may associate with infant birth outcomes. Results from the study herein revealed that hair cortisol in mid and late pregnancy was not associated with gestational age, when controlling for pre-pregnancy BMI. These findings are in contrast with a much larger study demonstrating a positive correlation between hair cortisol (measured at delivery) and gestational age (Kramer et al., 2009). In that sample of women (N=117), cortisol concentrations were significantly higher in the hair of women who delivered at term (mean = 190.6 (SD, 99.0) ng/g) than in those who delivered at <34 weeks of gestation (148.6 (SD, 39.2) ng/g). Others also found maternal hair cortisol at early, mid and late pregnancy to be positively correlated with infant birthweight (Karlen et al., 2013). While Kramer (2009) found hair cortisol to be positively correlated with gestational age, it was measured at delivery. It is possible that the levels of hair cortisol at delivery (i.e., term) simply reflect the normal increase in cortisol that occurs as pregnancy advances. In contrast, the lower hair cortisol in women with preterm delivery may reflect the shortened gestational time needed for cortisol to increase physiologically, as opposed to reflecting differences in maternal stress response activation (Kramer et al., 2009). This thinking is consistent with Kramer's lack of finding any association of hair cortisol with pregnancy-specific anxiety or other stress response measures (Kramer et al., 2001).

Moreover, findings from the present study also showed that childhood adversity interacted with hair cortisol levels at late-pregnancy (T2) to influence both birthweight and gestational age. These results showed that women exposed to higher levels of childhood adversity in combination with higher hair cortisol had infants with greater birthweight and increased gestational age. In contrast, women in late pregnancy with lower levels of childhood adversity exhibited no association between hair cortisol and birthweight or gestational age. However, given the small sample size in this analysis, caution should be used in interpreting this data.

In summary, evaluation of the association of maternal hair cortisol with pregnancy outcomes is in the early stages of investigation. Prospective, longitudinal studies with larger sample sizes are needed, as there are likely many covariates that influence levels of hair cortisol across pregnancy. This is best exemplified by a recent study, which measured maternal hair cortisol in the last trimester of pregnancy. That study found significantly higher cortisol concentrations in obese compared to normal weight and in smoking as opposed to non-smoking pregnant women. In contrast, women who delivered by cesarean section had lower hair cortisol compared to spontaneous delivery. Seasonal relationships were also observed, with higher hair cortisol in summer and autumn versus winter. Additionally, maternal education, numbers of persons in the household, premature delivery, and hair characteristics were associated with levels of hair cortisol (Braig et al., 2015). As the study by Braig et al. (2015) demonstrates, hair cortisol can be influenced by many factors, and the findings from the present study must be interpreted with caution.

Limitations

This study, conducted to fulfill requirements for a Ph.D. in nursing, has several limitations. An important limitation is the subject attrition from mid (T1) to late (T2) pregnancy; the reasons for this attrition are not known. Further, it is not clear if women who withdrew from the study had greater levels of perceived stress, depressive symptoms, or mood disturbance; prompting their withdrawal from the study. Ideally, evaluating women across pregnancy over three or more time points (as opposed to two time points) would have allowed use of hierarchical linear modeling (HLM) (K. E. Grant et al., 2003; K.A. Grant et al., 2010). HLM allows for analysis of subjects with incomplete and unbalanced data across time points, increasing statistical power and reducing bias. Also, HLM permits the ability to evaluate trajectories of individual differences among participants at study entry and across pregnancy and postpartum; this may allow greater understanding of heterogeneity among subjects. Furthermore, HLMs treat time as a continuous variable letting both time-variant and time-invariant covariates to be included in the model. In the present study, because of missing data, outcomes for some of the measures (especially those with greater variability) likely lacked sufficient power to detect significance. In particular, a number of women declined to provide hair samples for measurement of hair cortisol; this was especially the case for African American women and is a limitation of the study, especially in light of the very recent findings that maternal childhood adversity directly associated with hair cortisol only in African American women (Schreier et al., 2015).

As noted, the sample enrolled into this study comprised predominately White, well-educated, and middle class women; and most pregnancies were perceived positively. Accordingly, the insufficient numbers of lower income and minority women, who likely experience more childhood and current life adversity, limited detection of significant relationships. Further, the low numbers of these women prevented the evaluation of differences in outcomes based on race and ethnicity. Disadvantaged minority women are at greater risk for perinatal depression, as well as lower birthweight and premature infants; and thus represent a more vulnerable population. In the current sample, about half of the women reported depressive symptoms at or above the cut-scores; however, the incidence of premature birth and low birthweight was small, precluding stratifying births as 'premature,' 'low birthweight' and 'very low birthweight,' using clinical designations for these strata. As such, the generalizability of the results of the present study is limited to women who are at lower risk for delivery of either premature or low birth weight infants. Nevertheless, the findings are a first step toward a more comprehensive understanding of the associations among childhood adversity and maternal prenatal PNI profile and birth outcomes.

The National Institute for Health (NIH) stipulates for any clinical research projects that Ethnicity (Hispanic Latino or not Hispanic or Latino be asked first, then race asked to represent the five designated categories (White, Black or African American, Asian, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander) and allow the respondent to select more than one race (Wallman, 1997). When this research was conceptualized, I used the combination of race ethnicity given this is what

was listed in nearly all of the research studies and continues to be used. In future research, I will list as advised on the NIH guidelines to provide complete ethnic and race information for study participants.

Another limitation was the use of a retrospective measure of childhood adversity (i.e., CTQ), which relies upon the memory of participants, as well as their willingness to disclose adverse events. Although it is possible that retrospective assessment of early life experiences can have a high level of false-negative rates (Hardt & Rutter, 2004), the Childhood Trauma Questionnaire is considered a valid measure with wide use (Paivio, 2001). Furthermore, the degree of adversity is often underreported due to either suppression of memory of traumatic events or embarrassment to admitting adverse life experiences. Thus, if anything, adverse events are likely more frequent and of greater intensity than reported by this sample of women.

Additionally, this study assessed pre-pregnancy BMI by self-report. It is possible that women may underreport their body weight, compromising this measure, which was used to normalize levels of IL-6 and TNF-alpha. Lastly, the time domains for psychometric instruments varied from one instrument to another and may have limited findings. For example, the PSS (perceived stress) and PSQI (sleep quality) asked respondents to rate levels of stress and sleep, respectively, over the past month; other psychometric instruments asked respondents to assess levels of depressive mood (CES-D) and mood disturbance (POMS) over the past week, and the STAI (state anxiety) asked respondents to indicate how they feel at the moment. In contrast, the blood samples for proinflammatory cytokines likely reflect the levels for that particular day. Such

dissonance in time domain across measures may have limited finding significant associations among variables.

Conclusions and Implications

This investigation evaluated a community sample of healthy women during pregnancy to better understand the impact of stressors (across pregnancy) on maternal, psychological, circulating proinflammatory cytokines (IL-6, TNF alpha), as well as on neuroendocrine function (hair cortisol); and further to explore the impact of these on neonatal outcomes. Moreover, the contribution of maternal exposure to childhood adversity (as a predictor variable) and social support (as a moderating variable) were evaluated. Despite the above noted limitations, the findings of this study contribute to the evidence supporting the negative impact of psychological stressors on maternal mental health and infant birthweight and gestational age. In particular, the results add new knowledge as to the influence of maternal childhood adversity on maternal mental health during pregnancy. Women who were exposed to greater childhood adversity were shown to experience increased maternal prenatal stress perception, anxiety, mood disturbance, poor sleep, and risk for depression during pregnancy. Few previous studies have evaluated maternal childhood adversity as a risk factor during pregnancy, and as such, these findings can generate greater understanding for what makes certain women more susceptible to the challenges associated with pregnancy and future motherhood. Moreover, these initial findings can drive future research to investigate cumulative life stressors and apply an allostatic load framework to understand maternal bio-behavioral adaptation to pregnancy.

The findings also emphasize the interaction between maternal childhood adversity and increased proinflammatary cytokines and the risk for lower birthweight and earlier gestational age. That is, women who experienced higher levels of maternal childhood adversity and who had higher levels of plasma IL-6 delivered infants at earlier gestational age and with lower birthweight. Childhood adversity has been shown to engender a proinflammatory phenotype in non-pregnant individuals (Danese et al., 2007). However, this is likely the first such finding in pregnant women. These findings suggest that one way whereby maternal childhood adversity may negatively impact birth outcomes is through interacting with elevation of proinflammatory cytokines. The health implications are significant given that infant birthweight and gestational age are strong predictors of adult health over the life span. Thus, these results emphasize that a mother's history of childhood adversity can have major consequences for the next generation's health. As a whole, fhese findings emphasize the interplay of biolgical, psychological and social factors in poor birth outcomes, and extend understanding of predictors of poor birth outcomes. For health practitioners, these findings highlight the need to identify early life risk exposure, such as childhood adversity, which may negatively affect maternal mental health and the course of gestation. This is even more critical as evidence demonstrates that a history of childhood abuse is associated with a greater risk of being a victim of all types of abuse as an adult, with re-victimization occurring in a dose response manner (Chiu et al., 2013); and domestic violence during pregnancy is a major public health issue affecting the mother and the unborn child (Jahanfar, Howard, & Medley, 2013). Thus, implementing a life course perspective within prenatal (or pre-conceptual) care practice

can broaden maternal risk assessment, target vulnerable women, and foster tailored interventions. As such these findings are a first step in understanding the negative sequlae of maternal childhood adversity, and can serve as impetus for future research to include the examination of psychosocial risk antecedent to a women's pregnancy, including experience of early life adversity, to understand preterm and low birthweight. This is in line with the recent call for prenatal care delivery practices that allow for an understanding of the impact of trauma on a woman's life and future mental health. Such trauma-informed care, provided in a trusted environment, can pave the way for recovery from such traumatic experiences (Torchalla, Linden, Strehlau, Neilson, & Krausz, 2015). Success of preventive interventions for mother and child is exemplified by the work of David Olds who pioneered the use of a nurse home visiting program (Nurse-Family Partnership), which over many years has proved successful in improving the health and social conditions of vulnerable pregnant women and their families (Olds et al., 2014).

Social support emerged as an important variable that can influence maternal psychological well-being and infant outcomes. Importantly, the results of the present study suggest that harmful effects of maternal childhood adversity on birthweight and gestational age are even worse for women with low social support during their pregnancy. These findings provide impetus for health care providers to include an assessment of levels of social support in pregnant women during risk stratification, and to implement approaches that enable vulnerable women to develop sustainable and meaningful social support networks early on in pregnancy (or even when pregnancy is planned). The latter may take place in prenatal classes or even through use of technology

in which women can access peer support or support from trusted health care professionals. Another example is to foster prenatal family support groups and to provide child care for pregnant women with children, increasing their ability to attend prenatal programs. Future studies are needed that address additional resilience factors, such as spirituality, and the meaning women associate with being pregnant and parenting. An evaluation of faith based prenatal support groups may prove to be especially beneficial for African American women. Such research can lead to innovative models of care, which aim at increasing a woman's well-being and resilience, supporting them in their adaptive capacity during pregnancy and as new mothers.

An alternative and promising strategy to improve pregnancy outcomes is computer tailoring, an intervention in which advice is not delivered face-to-face, but via a computer (Lustria, Cortese, Norar, & Glueckauf, 2009). Although the content of this advice is computer-generated, it is tailored based on individual responses to questions. Accordingly, the feedback messages are adapted to the unique situation of the individual. This approach has been shown to be effective in promoting health behavior change in a variety of populations (Krebs, Prochaska, & Rossi, 2010) and recently in counseling pregnant women to reduce alcohol intake (van der Wulp et al., 2014).

This study was unique in that a Distress Composite Score was derived and used in regression analyses. Most importantly, findings revealed that women with higher Distress Composite Scores had higher circulating levels of IL-6. Further, the findings revealed that women exposed to higher levels of childhood adversity together with higher Distress Composite Scores delivered infants with lower birthweight and earlier

gestational age (i.e., earlier delivery). These findings suggest that the use of a more comprehensive index of the perception of psychological stressors and the emotional response to stressors during pregnancy will yield greater insight as to how psychological variables affect maternal and infant health outcomes.

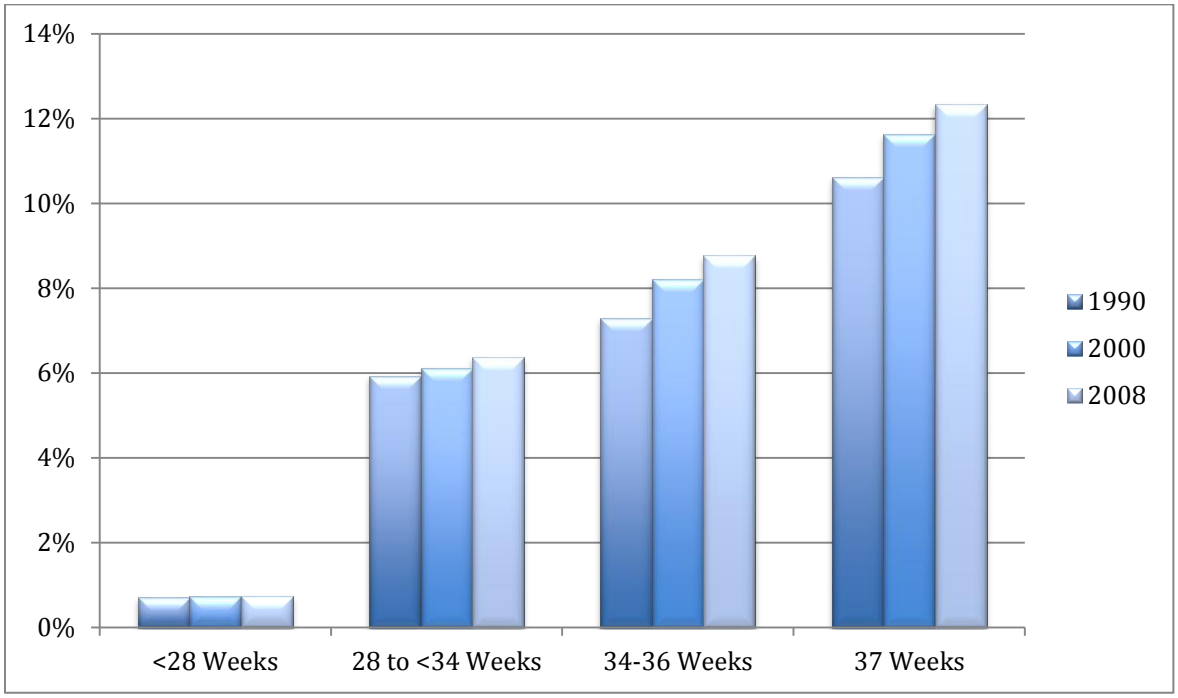
Another unique finding of this study was that women who experienced higher levels of childhood adversity reported greater sleep disturbance than those experiencing lower levels of childhood adversity. Poor sleep may predispose to psychological morbidity, especially perinatal depression. Moreover, poor sleep during late pregnancy was associated with poor neonatal outcomes (lower birthweight and earlier gestational age) but did not meet significance using a Bonferroni correction. Thus, these data support the need to provide information regarding strategies to improve maternal sleep quality, which in the end can benefit maternal health and infant development.

In summary, the findings from this dissertation research highlight the importance of utilizing a PNI framework to provide an integrated bio-behavioral understanding of the impact of maternal perception of psychological stressors on the adaptation to pregnancy. In particular, this study revealed unique findings that demonstrated that exposure to adversity early in life has long-lasting effects that influence perceived stress levels, anxiety, and depressive mood during pregnancy; and that this may disrupt inflammatory and neuroendocrine regulation needed for optimal maternal-infant health outcomes. Further, the findings emphasize the potential for social support to buffer the negative impact of maternal childhood adversity. Such knowledge can contribute to improved approaches to identify and stratify risk for adverse maternal-infant health outcomes, as

well as guide the development of early intervention programs and health policy for women who are pregnant or who plan to become pregnant (i.e., pre-conception counseling and care). It is vital that risk assessment extends beyond the window of pregnancy and includes assessment of vulnerability factors antecedent to pregnancy—a lifespan approach. Ultimately, such evidenced-based practice will have major health significance, as the well-being of mothers and infants determines the health of the next generation.

APPENDIX A

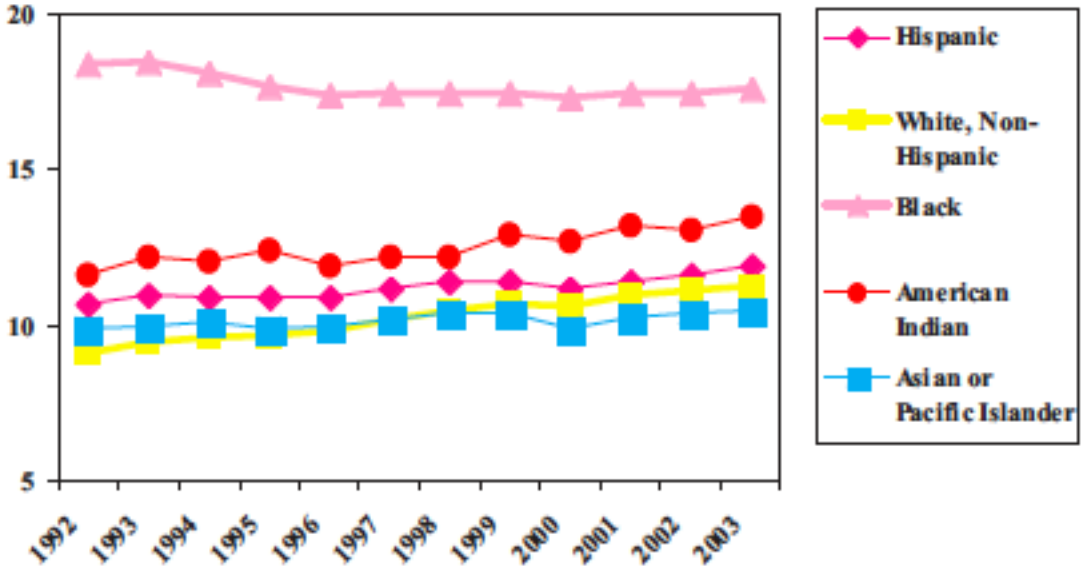
PERCENTAGES OF PREMATURE DELIVERIES BY GESTATION



(Martin et al., 2010).

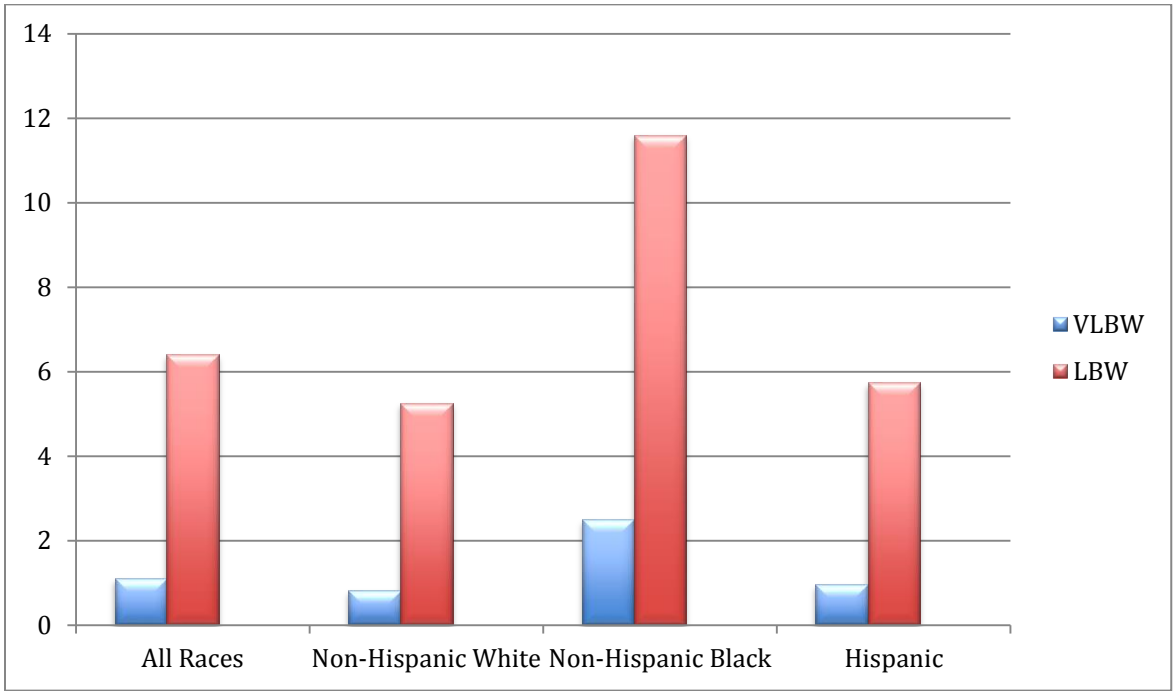
APPENDIX B

PRETERM BIRTH AS A PERCENTAGE OF LIVE BIRTHS, BY RACE AND ETHNICITY, 1992 TO 2003


20
15
10
5
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Hispanic
White, Non-Hispanic
Black
American Indian
Asian or Pacific Islander

APPENDIX C

RATES OF VERY LOW BIRTHWEIGHT (VLBW) AND LOW BIRTHWEIGHT (LBW) IN PREMATURE INFANTS, BY RACE AND ETHNIC ORIGIN (2008 DATA)



(Martin et al., 2010)

APPENDIX D

EXAMPLES OF THE TYPES OF STRESS EXPOSURE DURING PREGNANCY AND ASSOCIATION WITH A RANGE OF NEURODEVELOPMENTAL OUTCOMES

Table 1. Examples of the types of stress exposure during pregnancy, and association with a range of neurodevelopmental outcomes

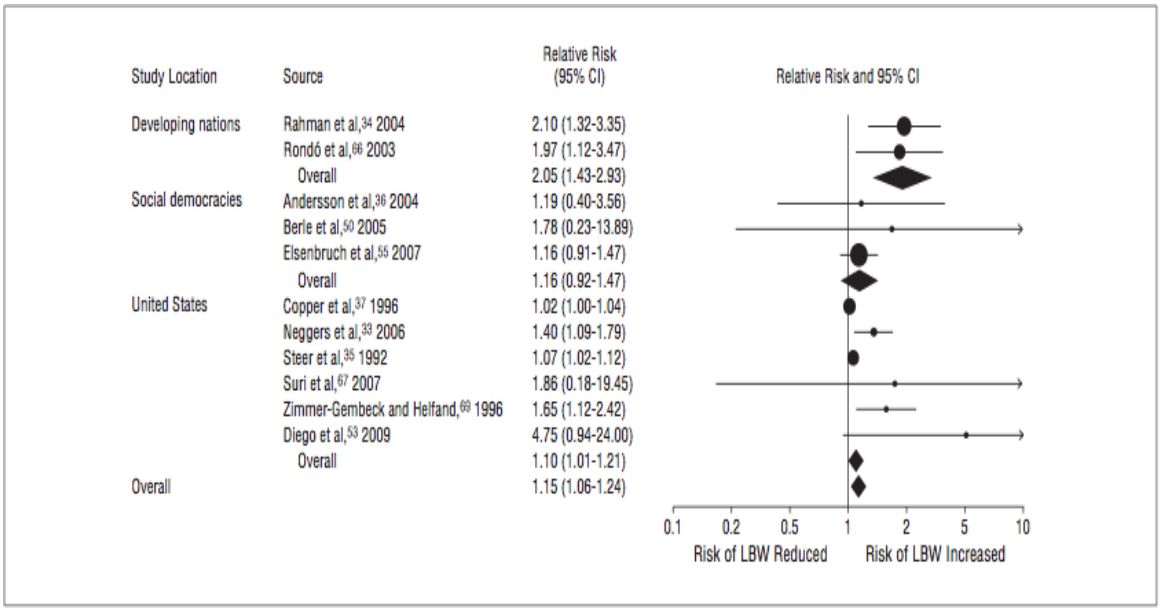
Type of exposure	Prenatal timing weeks	Outcome	Age	Magnitude	Citation
Perceived stress	10	ADHD (DSM-IV)	7–8 years	23% (v) †	Rodriguez and Bohlin [57]
Anxiety (state)	12–22	ADHD (CBCL, TRF)	8–9 years	22% (v)	Van den Bergh and Marcoen [13]
		sustained attention (CPT)	15 years	–[a]	Van den Bergh et al. [58]
Anxiety (trait)	–	depression (CDI)	15 years	–[b]	Van den Bergh et al. [59]
Perceived stress	15–38	behavioral problems (CBCL)	2 years	1.12–1.17(OR)	Gutteling et al. [60]
Daily hassles	15–17	mental development (BSID-MDI)	8 months	1.1 (OR)	Huizink et al. [7]
Pregnancy-related anxiety	15–38	temperament (ICQ) attention regulation (BSID)	2 years	1.39 (OR) 1.46 (OR)	Gutteling et al. [60]
Depression	–	attentiveness (NBAS)	neonate	–	Hernandez-Reif et al. [61]
Anxiety	32	emotional and behavioral problems (SDQ)	4 and 7 years	1.9–2.2 (OR)	O'Connor et al. [5, 6]
Life events stress	15–17	memory (TOMAL)	6 years	–	Gutteling et al. [30]
Life events stress (especially relationship problems)	–	cognitive development (BSID-MDI) fear reactivity (Lab-TAB)	1.5 years	17% (v) 10% (v)	Bergman et al. [12]
Death of a close relative	0–12	schizophrenia (ICD8/ICD10)	–	1.67 (OR)	Kashan et al. [1]
Hurricane	24–40	autism (DSM-III-R/DSM-IV)	–	10.12–43.05 (OR)	Kinney et al. [2]
Ice storm	4–24	cognitive developmental (BSID-MDI)	2 years	11.4% (v)	Laplante et al. [3]
	–	language production (MCDI)		17.3% (v)	
		IQ (WISC)	5.5 years	15.3 % (v)	Laplante et al. [4]
Chernobyl	14 →	depression/MDD (C-SSAGA-A: DSM-III-R)	14 years	2.48 (OR)	Huizink et al. [62]
		ADHD		2.01 (OR)	
9/11	–	temperament (IBQ)	9 months	–	Brand et al. [63]

v = Amount of variance explained; OR = odds ratio; ADHD = attention deficit and hyperactivity disorder; DSM-R = diagnostic and statistical manual-revised; CBCL = child behavior checklist; TRF = teacher's report form; CPT = continuous performance task; CDI = child depression inventory; BSID = Bayley's scale of infant development; MDI = mental development index; ICQ = infant characteristics questionnaire; NBAS = Brazelton neonatal behavioral assessment scale, SDQ = strengths and difficulties questionnaire; TOMAL = test of memory and learning; Lab-TAB = laboratory temperament assessment battery; ICD = international classification of diseases; MCDI = MacArthur communicative development inventory; IQ = intelligence quotient; WPPSI = Wechsler preschool and primary scale of intelligence; MDD = major depressive disorder; C-SSAGA-A = child semistructured assessment of genetics of alcoholism; IBQ = infant behavior questionnaire; [a] in boys only; [b] in girls only; – = not reported.

(O'Donnell, 2009).

APPENDIX E

EFFECT OF ANTENATAL DEPRESSION ON THE RISK OF LOW BIRTHWEIGHT (LBW) IN DEVELOPING NATIONS, EUROPEAN SOCIAL DEMOCRACIES, AND THE UNITED STATES



(Grote et al., 2010)

APPENDIX F

SCHEMATIC ILLUSTRATION OF CONNECTIONS BETWEEN THE NERVOUS AND IMMUNE SYSTEMS

(Sternberg, 2006)

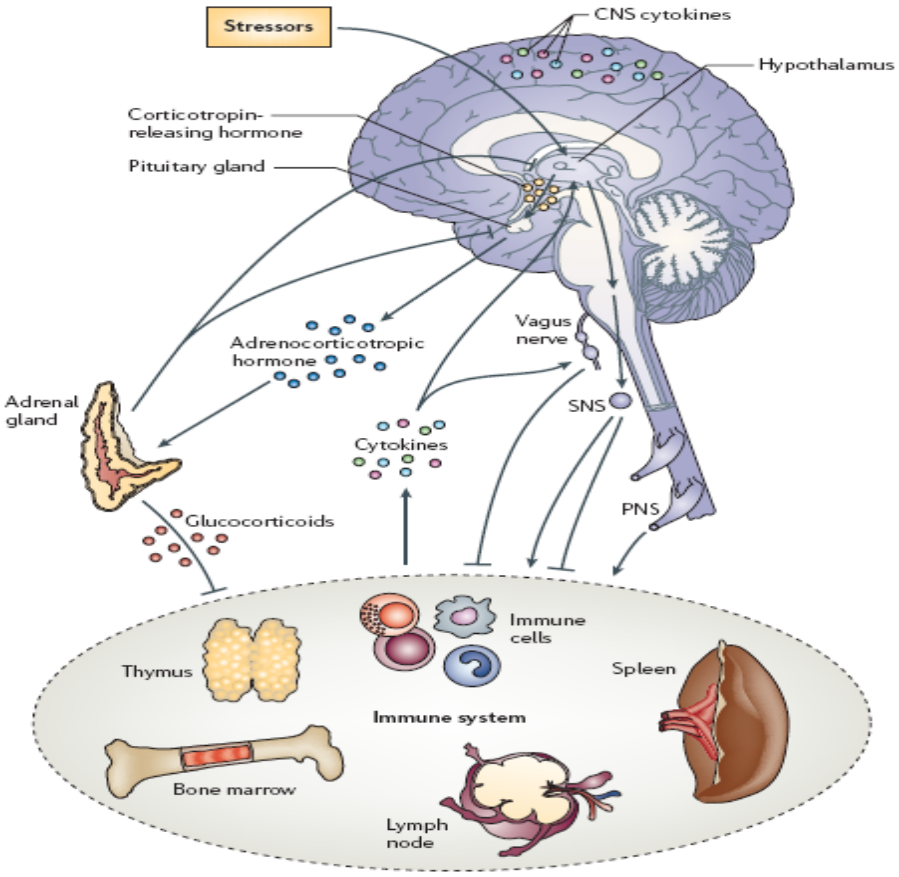


Figure 1 | **Schematic illustration of connections between the nervous and immune systems.** Signalling between the immune system and the central nervous system (CNS) through systemic routes, the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS) and the peripheral nervous system (PNS) are shown. Figure modified with permission from *Molecular Psychiatry* REF. 140 © (2005) Macmillan Magazines Ltd.

APPENDIX G

REGULATION OF THE HPA AXIS ACROSS PREGNANCY IMPLICATIONS FOR MOTHER-INFANT HEALTH OUTCOMES

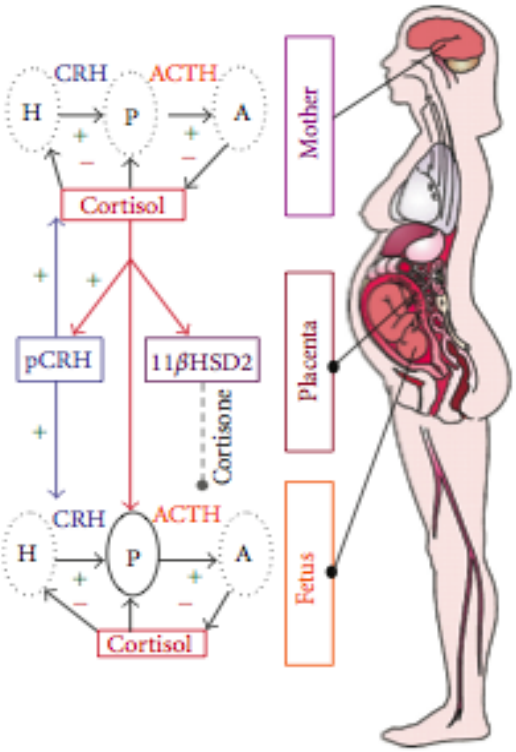


FIGURE 1: The regulation of the HPA axis changes dramatically over the course of gestation with profound implications for the mother and the fetus. One of the most significant changes during pregnancy is the development of the placenta, a fetal organ with significant endocrine properties. During pregnancy, CRH is released from the placenta into both the maternal and fetal compartments. In contrast to the negative feedback regulation of hypothalamic CRH, cortisol *increases* the production of CRH from the placenta. Placental CRH (pCRH) concentrations rise exponentially over the course of gestation. In addition to its effects on pCRH, maternal cortisol passes through the placenta. However, the effects of maternal cortisol on the fetus are modulated by the presence of p11βHSD2 which oxidizes it into an inactive form, cortisone. Activity of this enzyme increases as pregnancy advances and then drops precipitously so that maternal cortisol is available to promote maturation of the fetal lungs, central nervous system, as well as other organ systems.

APPENDIX H

DATA COLLECTION TOOLS

Demographic Information Form

Date of Birth _____/_____/_____
Month/day/year

1. **Race/Ethnic Group**:

_____White _____Native Hawaiian or Other Pacific Islander
_____African American _____Other_____
_____Hispanic/Latina _____Asian
_____American Indian/Alaska Native _____More Than One Race

2. **Marital Status**: _____Single
_____Married
_____Divorced/Separated
_____Widowed
3. **Education:** (Please circle the highest level of education completed in each category that applies to you)

High School: 9 10 11 12
College: 1 2 3 4
Graduate School: 1 2 3 4 5 6 7 8
Vocational/Technical School: 1 2 3 4
Other (please specify)_____

4. **Current Employment:** (Please check all that apply to you)
_____Full time
_____Part time (Hours/week_____)
_____Employed and work at home
_____Homemaker
_____Unemployed
_____Student
_____Other
5. What is your usual occupation? _____
6. What is your total household income?
_____less than $9,999
_____$10,000to$19,000
_____$20,000 to $29,000
_____$30,000 to $39,000
_____$40,000 to $49,000
_____$50,000 to $59,000
_____$60,000 to $69,000
_____$70,000 and higher
7. How many people/dependents live off this income? _____

Pregnancy Health Assessment Survey (HAS) (developed from MIHA, 2009 and PRAMS)
Please answer questions or circle response.

1 Today's Date mo/day/year
2 Due date by last menstrual period mo/day/year
Due date by Ultrasound mo/day/year
4 How many times have you been pregnant? _____
How many miscarriages have you had? _____
5 How many biologic children do you have? _____
6 Did you ever have a baby that weighted less than 5 lbs., 8oz (2.5kg) at birth? Yes / No
7 Did you ever have a baby that was born prematurely (born before 37 weeks of pregnancy)? Yes / No
8 What was your birthweight? ____ lbs _____ don't know
9 Did you ever have a Cesarean delivery or C-section? Yes / No
10 Before this pregnancy have you ever received WIC (Women, Infant, and Children supplementary food program)? Yes / No
11 Did you have regular health care in the year before this pregnancy? Yes / No
12 Did you need fertility treatment for this pregnancy? Yes / No
13 What type of health care coverage did you have just prior to getting pregnant?
No Health Insurance Private Insurance (i.e. BC/BS; HMO)
Public Insurance Combined Public and Private
14 How would you rate your *Physical Health* just prior to getting pregnant?
Excellent / Good / Fair / Poor
15 How would you rate your *Mental Health* just prior to getting pregnant?
Excellent / Good / Fair / Poor
16 What was your pre-pregnancy weight?
17 What is your current weight?
18 What is your height
19 In the month before you got pregnant, how many times a week did you take a multivitamin, prenatal vitamin, or folic acid?
Never / 1-3 times/week / 4-6 times/wk. / Daily
20 In the last month, how many times a week do you take a multivitamin, prenatal vitamin, or folic acid?
Never / 1/3 times/wk. / 4-6 times/wk. / Daily
21 When you got pregnant, were you using birth control (condoms, birth control pills, shots or another method? Yes No
22 Was this pregnancy was planned? Yes No
23 When did you find out you were pregnant?
#weeks _____ #months _____
24 When your pregnancy was confirmed, how did you feel?
Very happy / Somewhat happy / Somewhat Unhappy / Very Unhappy
Unsure how I felt

25 **Before you got pregnant, did you have…**? (**Check if you took medication)**

Diabetes (high blood sugar)	Yes	No
Hypertension (high blood pressure)	Yes	No
Anemia	Yes	No
Thyroid problems	Yes	No
Asthma	Yes	No
Depression	Yes	No
Anxiety	Yes	No
Eating disorder (anorexia, bulimia, etc)	Yes	No

26 **During your current pregnancy, do you have… Check if you took medication)**

Diabetes (high blood sugar)	Yes	No
Hypertension (high blood pressure)	Yes	No
Anemia	Yes	No
Thyroid problems	Yes	No
Asthma	Yes	No
Depression	Yes	No
Anxiety	Yes	No
Eating disorder (anorexia, bulimia, etc)	Yes	No

27 **Current health problems…**

Labor pains before 37 weeks of pregnancy	Yes	No
Water broke before 37 weeks of pregnancy	Yes	No
Pre-eclampsia, eclampsia, or toxemia	Yes	No
Placental problems (i.e. Abruptio placenta, placenta previa, low-lying placenta)	Yes	No
Cervical problems needing a cerclage (cervix sewn shut) because of an incompetent cervix.	Yes	No

Other problems? Explain

28 **Prenatal Care: or Health Care for Pregnancy**

When did you start getting prenatal care? # weeks # months

During this pregnancy, did any health care worker suggest you get testing for a birth defect in your baby?	Yes	No	Not Sure
If yes, did you have the testing done?	Yes	No	Not Sure

What tests did you have during this pregnancy?

AFP or expanded AFP test	Yes	No	Not Sure
Amniocentesis or amnio (putting a needle in your belly to sample the amniotic fluid around the baby	Yes	No	Not Sure
CVS (chronic villi sampling) to take a tiny piece of placenta	Yes	No	Not Sure
NT (nuchal translucency) (an ultrasound to measure thickness of the baby's neck)	Yes	No	Not Sure

Other test: please describe

29. **Did any of these events happen to you during this pregnancy?**

Separated or divorced from partner	Yes	No
Moved to a new address	Yes	No
Homeless (sleeping outside, in car, or in homeless shelter	Yes	No
Husband or partner lost their job	Yes	No
I lost my job, even though I wanted to continue working	Yes	No
I have many bills I cannot pay	Yes	No
My partner went to jail	Yes	No
Someone very close to me has problems with drugs or alcohol	Yes	No

30 **Health Questions: Right now during pregnancy**

Do you smoke?	Yes	No
How many cigarettes/day?	_____	
Do you drink alcohol?	Yes	No
How many drinks/day	_____	
Do you drink caffeinated drinks?	Yes	No
How many drinks/day (8 oz. drinks)	_____	

31 **After delivery how do you intend to feed your baby?**

Breast feed	Yes	No	Not Sure
Bottle feed	Yes	No	Not Sure
Combination Breast and Bottle	Yes	No	Not Sure

If you plan to Breast feed, how long are you planning to do this?
weeks / months _____

Were you breast fed as an infant	Yes	No
Do any of your friends breast feed their infants?	Yes	No

32 **Describe your pregnancy overall:**

One of the happiest times of my life
Happy time without many problems
Moderately hard time
Very hard time
One of the worse times of my life

33 **Please describe any events during this pregnancy that were stressful to you.**

34 **Please explain what you worried about during this pregnancy.**

Perceived Stress Scale (PSS) (S. Cohen et al., 1988)

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by circling how often you felt or thought a certain way.
0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1	In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2	In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3	In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4	In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5	In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6	In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7	In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8	In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9	In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10	In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Profile of Mood States (POMS-65) (McNair et al., 1992 1971)

Directions: Describe HOW YOU FEEL RIGHT NOW by checking one space after each of the words listed below:

FEELING
1.Not at all
2. A little
3. Moderate
4. Quite a bit
5. Extremely

1	Friendly	1	2	3	4	5
2	Tense	1	2	3	4	5
3	Angry	1	2	3	4	5
4	Worn Out	1	2	3	4	5
5	Unhappy	1	2	3	4	5
6	Clear-headed	1	2	3	4	5
7	Lively	1	2	3	4	5
8	Confused	1	2	3	4	5
9	Sorry for things done	1	2	3	4	5
10	Shaky	1	2	3	4	5
11	Listless	1	2	3	4	5
12	Peeved	1	2	3	4	5
13	Considerate	1	2	3	4	5
14	Sad	1	2	3	4	5
15	Active	1	2	3	4	5
16	On Edge	1	2	3	4	5
17	Grouchy	1	2	3	4	5
18	Blue	1	2	3	4	5
19	Energetic	1	2	3	4	5
20	Panicky	1	2	3	4	5
21	Hopeless	1	2	3	4	5
22	Relaxed	1	2	3	4	5
23	Unworthy	1	2	3	4	5
24	Spiteful	1	2	3	4	5
25	Sympathetic	1	2	3	4	5
26	Uneasy	1	2	3	4	5
27	Restless	1	2	3	4	5
28	Unable to Concentrate	1	2	3	4	5

29	Fatigued	1	2	3	4	5
30	Helpful	1	2	3	4	5
31	Annoyed	1	2	3	4	5
32	Discouraged	1	2	3	4	5
33	Resentful	1	2	3	4	5
34	Nervous	1	2	3	4	5
35	Lonely	1	2	3	4	5
36	Miserable	1	2	3	4	5
37	Muddled	1	2	3	4	5
38	Cheerful	1	2	3	4	5
39	Bitter	1	2	3	4	5
40	Exhausted	1	2	3	4	5
41	Anxious	1	2	3	4	5
42	Ready to Fight	1	2	3	4	5
43	Good-natured	1	2	3	4	5
44	Gloomy	1	2	3	4	5
45	Desperate	1	2	3	4	5
46	Sluggish	1	2	3	4	5
47	Rebellious	1	2	3	4	5
48	Helpless	1	2	3	4	5
49	Weary	1	2	3	4	5
50	Bewildered	1	2	3	4	5
51	Alert	1	2	3	4	5
52	Deceived	1	2	3	4	5
53	Furious	1	2	3	4	5
54	Effacious	1	2	3	4	5
55	Trusting	1	2	3	4	5
56	Full of Pep	1	2	3	4	5
57	Bad-tempered	1	2	3	4	5
58	Worthless	1	2	3	4	5
59	Forgetful	1	2	3	4	5
60	Carefree	1	2	3	4	5
61	Terrified	1	2	3	4	5
62	Guilty	1	2	3	4	5
63	Vigorous	1	2	3	4	5
64	Uncertain about Things	1	2	3	4	5
65	Bushed	1	2	3	4	5

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
- ☐ Yes, all the time
- ☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
- ☐ No, not very often — Please complete the other questions in the same way.
- ☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often

*5 I have felt scared or panicky for no very good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

*6. Things have been getting on top of me
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

*8 I have felt sad or miserable
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

*9 I have been so unhappy that I have been crying
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

*10 The thought of harming myself has occurred to me
   - Yes, quite often
   - Sometimes
   - Hardly ever
   - Never

Administered/Reviewed by _____ Date _____

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

Pregnancy Experience Scale-Brief (PES-Brief)
(J. A. DiPietro, Christensen, A. L., & Costigan, K. A., 2008)

Below are 10 items that you may consider to be uplifting aspects of your pregnancy and 10
items that may be less appealing. Please circle the degree to which each item

0 = Not at all 1 = Somewhat 2 = Quite a bit 3 = A great deal

How much have each of the following made you feel happy, positive, or uplifted?

1	How much is the baby moving	0	1	2	3
2	Discussion with spouse about baby names	0	1	2	3
3	Comments from others about your pregnancy/appearance	0	1	2	3
4	Making or thinking about nursery arrangements	0	1	2	3
5	Feelings about being pregnant at this time	0	1	2	3
6	Visits to obstetrician/midwife	0	1	2	3
7	Spiritual feelings about being pregnant	0	1	2	3
8	Courtesy/assistance from others because you are pregnant	0	1	2	3
9	Thinking about the baby's appearance	0	1	2	3
10	Discussions with spouse about pregnancy/childbirth issues	0	1	2	3

How much have each of the following made you feel unhappy, negative, or upset?

1	Getting enough sleep	0	1	2	3
2	Physical intimacy	0	1	2	3
3	Normal discomforts of pregnancy	0	1	2	3
4	Your weight	0	1	2	3
5	Body Changes due to pregnancy	0	1	2	3
6	Thoughts about whether the baby is normal	0	1	2	3
7	Thinking about your labor and delivery	0	1	2	3
8	Ability to do physical tasks/chores	0	1	2	3
9	Concerns about physical symptoms (pain, spotting, etc)	0	1	2	3
10	Clothes/shoes don't fit	0	1	2	3

APPENDIX

Tilburg Pregnancy Distress Scale

The following questions relate to the way you perceive your pregnancy. **Circle** the **box** that best reflects how you felt during **the last 7 days**. Please circle only one answer to each question

		Very often	Fairly often	Now and then	Rarely or never
1.	I am enjoying my pregnancy	☐	☐	☐	☐
2.	I feel like my partner and I are enjoying the pregnancy together	☐	☐	☐	☐
3.	I worry about the pregnancy	☐	☐	☐	☐
4.	The pregnancy has brought my partner and I closer together	☐	☐	☐	☐
5.	I worry about the delivery	☐	☐	☐	☐
6.	I worry about the health of my baby	☐	☐	☐	☐
7.	I worry about my job once the baby is born	☐	☐	☐	☐
8.	I feel supported by my partner	☐	☐	☐	☐
9.	I worry about our financial situation after childbirth	☐	☐	☐	☐
10.	I am afraid I will lose self-control during delivery	☐	☐	☐	☐
11.	I often think about choices concerning the delivery	☐	☐	☐	☐
12.	The delivery is troubling me	☐	☐	☐	☐
13.	I get very tense hearing stories about deliveries	☐	☐	☐	☐
14.	I am concerned that the physical discomforts of pregnancy might persist after childbirth	☐	☐	☐	☐
15.	I can really share my feelings with my partner	☐	☐	☐	☐
16.	I worry about gaining too much weight	☐	☐	☐	☐

Key to calculate scores

Item : 3, 5, 6, 7, 9, 10, 11, 12, 13, 14 and 16 should be recoded (3=0, 2=1, 1=2, 0=3).

Sociodemographic Questionnaire

The MacArthur Network on SES and Health has developed a sociodemographic questionnaire, which is currently being used in a number of network sponsored projects. The instrument begins with subjective social status questions developed by the network; (see MacArthur Subjective Social Status Scale in the Psychosocial Notebook). The remaining questions assess educational attainment, occupational status, income and assets. Ideally, all questions would be used; if a subset must be selected, items 1, 2, 3, 4, 6b and 6c, 7 and 9 are recommended.

Question 1.

Think of this ladder as representing where people stand in their communities.

People define community in different ways; please define it in whatever way is most meaningful to you. At the **top** of the ladder are the people who have the highest standing in their community. At the **bottom** are the people who have the lowest standing in their community.

Where would you place yourself on this ladder?

Please place a large **"X"** on the rung where you think you stand at this time in your life, relative to other people in your community.

Question 2.

Think of this ladder as representing where people stand in the United States.

At the **top** of the ladder are the people who are the best off – those who have the most money, the most education and the most respected jobs. At the **bottom** are the people who are the worst off – who have the least money, least education, and the least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top; the lower you are, the closer you are to the people at the very bottom.

Where would you place yourself on this ladder?

Please place a large **"X"** on the rung where you think you stand at this time in your life, relative to other people in the United States.

Question 3. What is the highest grade or year of regular school you have complete?

Check box	Elementary	High School	College	Graduate School
	01	09	13	17
	02	10	14	18
	03	11	15	19
	04	12	16	20+
	05			
	06			
	07			
	08			

Question 4. What is the highest degree you earned?

Check Box	
	High school diploma or equivalency (GED)
	Associate Degree (Junior College
	Bachelor's Degree
	Master's Degree
	Doctorate
	Professional (MD,JD,DDS,etc.)
	Other (please specify)
	None of the above (less than High School)

Question 5. Which of the following best describes your current main daily activities and/or responsibilities?

Check Box	
	Working full time
	Working part-time
	Unemployed or laid off
	Looking for work
	Keeping house or raising children full time
	Retired

Question 6. With regard to your current or most recent job activity:

In what kind of business or industry do (did) you work?
(For example: hospital, newspaper publishing, mail order house, auto engine manufacturing, breakfast cereal manufacturing.)

What kind of work do (did) you do? (Job Title)
(For example: registered nurse, personnel manager, and supervisor of order department, gasoline engine assembler, and grinder operator.)

How much did you earn, before taxes and other deductions, during the past 12 months?

Check box	
	Less than $5,000
	$5,000 through $11,999
	$12,000 through $15,999
	$16,000 through $24,999
	$25,000 through $34,999
	$35,000 through $49,999
	$50,000 through $74,999
	$75,000 through $99,999
	$100,000 and greater
	Don’t know
	No response

Question 7. How many people are currently living household, including yourself?

	Number of people in household?
	Of these people, how many are children?
	Of these people, how many are adults?
	Of the adults, how many bring income into household?

Question 8. Is the home where you live:

Check Box	
	Owned or being bought by you (or someone in the household)?
	Rented for money?
	Occupied without payment of money or rent?
	Other (specify)

[Some might try to get a "market value" estimate of the value of owned homes and an estimate of how much principal was outstanding on the mortgage.]

Question 9. Which of these categories best describe your total combined income for the past 12 months?
This should include income (before taxes) form all sources, wages, rent from properties, social security, disability and or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on.

Check Box	
	Less than $5,000
	$5,000 through $11,999
	$12,000 through $15,999
	$16,000 through $24,999
	$25,000 through $34,999
	$35,000 through $49,999
	$50,000 through $74,999
	$75,000 through $99,999
	$100,000 or greater
	Don't know
	No response

Question 10. If you lost all your current source(s) of household income(your paycheck, public assistance, or other forms of income), how long could you continue to live at your current address and standard of living?

Check box	
	Less than 1 month
	1 to 2 months
	3 to 6 months
	7 5o 12 months
	More than 1 year

Question 11. Suppose you needed money quickly, and you cashed in all of your (and your spouse's) checking and savings accounts, and any stocks and bonds. If you added up what you would get, about how much would this amount to?

Check box	
	Less than $500
	$500 to $4,999
	$5,000 to $9.999
	$10,000 to $19,999
	$20,000 to $49,999
	$50,000 to $99,000
	$100,000 to $199,999
	$200,000 to $499,999
	$500,000 and greater
	Don't know
	No response

Question 12. If you now subtracted out any debt that you have (credit card debt, unpaid loans including car loans, home mortgage), about how much would you have left?

Check box	
	Less than $500
	$500 to $4,999
	$5,000 to $9.999
	$10,000 to $19,999
	$20,000 to $49,999
	$50,000 to $99,000
	$100,000 to $199,999
	$200,000 to $499,999
	$500,000 and greater
	Don't know
	No response

Social Provisions Scale

Instructions: Using the scale below, please circle the number after each statement that indicates how much each statement describes your situation. If you feel a statement is VERY TRUE, you would circle STRONGLY AGREE. If you feel a statement CLEARLY does not describe your relationships, you would answer STRONGLY DISAGREE.

1=STRONGLY DISAGREE
2= DISAGREE
3= AGREE
4=STRONGLY DISAGREE

1	There are people I know who will help me if I really need it	1	2	3	4
2	I do not have close relationships with others	1	2	3	4
3	There is no one I can turn to in times of stress	1	2	3	4
4	There are people who call on me to help them	1	2	3	4
5	There are people who like the same social activities I do	1	2	3	4
6	Other people do not think I am good at what I do	1	2	3	4
7	I feel responsible for taking care of someone else	1	2	3	4
8	I am with a group of people who think the same way I do about things	1	2	3	4
9	I do not think that other people respect what I do	1	2	3	4
10	If something went wrong, no one would help me	1	2	3	4
11	I have close relationships that make me feel good	1	2	3	4
12	I have someone to talk to about decisions in my life	1	2	3	4
13	There are people who value my skills and abilities	1	2	3	4
14	There is no one who have the same interested and concerns as me	1	2	3	4
15	There is no one who needs me to take care of them	1	2	3	4
16	I have a trustworthy person to turn to if I have problems	1	2	3	4
17	I feel a strong emotional tie with at least one other person	1	2	3	4
18	There is no one I can count on for help if I really need it	1	2	3	4
19	There is no one I feel comfortable talking about problems with	1	2	3	4
20	There are people who admire my talents and abilities	1	2	3	4
21	I do not have a feeling of closeness with anyone	1	2	3	4
22	There is no one who likes to do the things I do	1	2	3	4
23	There are people I can count on in an emergency	1	2	3	4
24	No one needs me to take care of them	1	2	3	4

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-1

Please provide the following information:

Name_____ Date_____ S_____

Age_____ Gender (*Circle*) **M** **F** T_____

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

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Subject Initials: _____ Subject #: _____ Visit Date: _____ Visit # _____ pg. 1

CTQ

When I was growing up…	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat	1	2	3	4	5
2. I knew that there was someone to take care of me and protect me.	1	2	3	4	5
3. People in my family called me things like "stupid," "lazy," or "ugly".	1	2	3	4	5
4. My parents were too drunk or high to take care of the family	1	2	3	4	5
5. There was someone in my family who helped me feel that I was important or special.	1	2	3	4	5
6. I had to wear dirty clothes.	1	2	3	4	5
7. I felt loved.	1	2	3	4	5
8. I thought that my parents wished I had never been born.	1	2	3	4	5
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
10. There was nothing I wanted to change about my family.	1	2	3	4	5
11. People in my family hit me so hard that it left me with bruises or marks.	1	2	3	4	5
12. I was punished with a belt, a board, a cord, or some other hard object.	1	2	3	4	5
13. People in my family looked out for each other.	1	2	3	4	5
14. People in my family said hurtful or insulting things to me.	1	2	3	4	5
15. I believe that I was physically abused.	1	2	3	4	5
16. I had a perfect childhood.	1	2	3	4	5
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	1	2	3	4	5
18. I felt that someone in my family hated me.	1	2	3	4	5
19. People in my family felt close to each other.	1	2	3	4	5
20. Someone tried to touch me in a sexual way, or tried to make me touch them	1	2	3	4	5
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	1	2	3	4	5
22. I had the best family in the world.	1	2	3	4	5
23. Someone tried to make me do sexual things or watch sexual things.	1	2	3	4	5
24. Someone molested me.	1	2	3	4	5
25. I believe that I was emotionally abused.	1	2	3	4	5
26. There was someone to take me to the doctor if I needed it.	1	2	3	4	5
27. I believe that I was sexually abused.	1	2	3	4	5
28 My family was a source of strength and support.	1	2	3	4	5

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month:

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) ___ _____

5	During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (Anum, Springel, Shriver, & Strauss)
	a. Cannot get to sleep within 30 minutes				
	b. Wake up in the middle of the night or early morning				
	c. Have to get up to use the bathroom				
	d. Cannot breathe comfortably				
	e. Cough or snore loudly				
	f. Feel too cold				
	g. Feel too hot				
	h. Have bad dreams				
	i. Have pain				
	j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6	During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				

7	During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8	During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
		Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (Anum, et al.)
9	During the past month, how would you rate your sleep quality overall?				
		No partner or roommate	Partner or roommate in other room	Partner or roommate in same room, not in same bed	Partner or roommate in same bed
10	Do you have a bed partner or roommate?				
	If you have a roommate or bed partner , ask him/her how often in the past week you had…	Not during past	Less than once a week	Once or twice a week	Three times or more a week
	a. loud snoring				
	b. Long pauses between breaths while asleep				
	c. leg twitching or jerking while you sleep				
	d. Episodes of disorientation or confusion during sleep				
	e. Other restlessness while you sleep; please describe				

Pregnancy Anxiety Scale (PAS) (Rini et al., 1999).

Instructions: Indicate the frequency or the extent to which you feel worried or concerned

1= Never or not at all
2= Some or a little of the time
3= Occasionally, or a moderate amount of the time
4= A lot of the time or very much

		Never or not at all	Some or a little of the time	Occasionally or a moderate amount of the time	A lot of the time or very much
1	I am confident of having a normal childbirth	1	2	3	4
2	I think my labor and delivery will go normally	1	2	3	4
3	I have a lot of fear regarding the health of my baby	1	2	3	4
4	I am worried that the baby could be abnormal	1	2	3	4
5	I am afraid that I will be harmed during delivery	1	2	3	4
6	I am concerned (worried) about how the baby is growing and developing inside me	1	2	3	4
7	I am concerned (worried) about losing the baby		2	3	4
8	I am concerned (worried) about having a hard or difficult labor and delivery	1	2	3	4
9	I am concerned (worried) about taking care of a new baby	1	2	3	4
10	I am concerned (worried) about developing medical problems during my pregnancy	1	2	3	4

Table 2. Tools and Data Collection Time Points.

	T1: 16-24 WEEKS GESTATION	T2: 28-32 WEEKS GESTATION	AFTER DELIVERY
BACKGROUND INFORMATION			
Demographic Information	X		
Health History Survey	X	X	
PRIOR LIFE ADVERSITY			
Childhood Trauma Questionnaire	X		
Household Dysfunction	X		
MacArthur Subjective Social Status Scale (MSS)	X		
MODERATING VARIABLES			
Social Provisions Assessment (SPA)	X	X	
PSYCHOLOGICAL DATA			
Perceived Stress Scale (PSS)	X	X	
Pregnancy Related Anxiety (PA)	X	X	
State Trait Anxiety (STAI)	X	X	
Edinburgh Depression Scale (EDS)	X	X	
Depressive Symptoms (CES-D)	X	X	
Mood Disturbance (POMS-65)	X	X	
Pregnancy Experience Scale (PES-Brief)	X	X	
Tilburg Pregnancy Distress Scale (TPDS)	X	X	
The Pittsburg Sleep Quality Index (PSQI)	X	X	
NEUROENDOCRINE DATA			
Hair cortisol (cutting hair)	X	X	
IMMUNE DATA			
IL-6 (blood draw)	X	X	
TNF alpha (blood draw)	X	X	
NEONATAL OUTCOMES			
Birthweight (grams)			X
Gestational Age (weeks gestation)			X

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