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Fetal Responsivity: Who's at Risk? Predicting Birth and Neurobehavioral Outcomes

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Fetal Responsivity: Who's at Risk? Predicting Birth and Neurobehavioral Outcomes

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Fetal Responsivity: Who's at Risk? Predicting Birth and Neurobehavioral Outcomes
By Joy D. Beckwith

The primary goal of the current study was to examine the ability of fetal responses, fetal heart rate (FHR) and fetal movement (FM) to predict adverse birth and neurobehavioral outcomes in relation to maternal stress during pregnancy. It was hypothesized that abnormal fetal responses, presumed to be due to maternal distress during pregnancy, would predict those at risk for low birth weight, gestational age, and Apgar scores, as well as less optimal neurobehavioral profiles on the Neonatal Behavioral Assessment Scale. Pregnant women (N=152) completed self-report measures of distress and underwent fetal monitoring at two prenatal time points, followed by two post-natal probes of newborn behavior at birth and one month postpartum. Regression analyses generally failed to demonstrate that fetal responses of heart rate and movement predicted adverse postnatal outcomes. However, baseline fetal heart rate did significantly predict postnatal abnormal reflexes and self-regulation. Maternal perception of stress also had modest correlations with fetal heart rate and movement post-stimulation, abnormal reflexes, and alertness. Methodological factors limiting the interpretation of these findings were discussed. Exploratory analyses suggested that continued exploration of maternal distress, fetal responses, and post-natal outcomes might be warranted, with particular attention given to potency of stimuli, measurement and perception of distress, and timing of experience. Reliable identification of pregnant women at risk for adverse post-natal outcomes remains an important objective as the field looks to provide prevention and early intervention efforts that have the potential to buffer the adverse effects of stress.

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"The race is not given to the swift, nor the battle to the strong but to he who endures to the end." Ecclesiastes 9:11.

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Fetal Responsivity: Who's at Risk? Predicting Birth and Neurobehavioral Outcomes

Pregnancy represents a time of significant physical and psychological change for women. Although most women adjust to these changes with little difficulty, it has been well established that others experience marked maternal distress, conceptualized as stress, depression, and/or anxiety, during the prenatal period (Blomberg, 1980; Emory & Dieter, 2006; Ferreira, 1965; Henrichs et al., 2010). In fact, it has been estimated that more than 500,000 pregnancies annually involve women who qualify as having a psychiatric illness (Dieter et al., 2008). Specifically, approximately 10-25% of pregnant women experience prenatal anxiety and/or depression (Anderson et al., 2004; Field, Diego, & Hernandez-Reif, 2006; Monk, 2001; Salisbury, 2010; Stowe, Hostetter, & Newport, 2005), with more than half experiencing it within their first trimester (Gavin, Gaynes, Lohr, Meltzer-Brady, & Garthlehrer, 2005). Distress during the prenatal period has not only been found to result in debilitating effects for the expecting mother (Emory & Dieter, 2006; Henrichs et al., 2010) but also potentially detrimental effects for the offspring (Brand & Brennan, 2009).

The prenatal period is seen as a critical time for the infant. The role of the prenatal environment in subsequent infant development and behavior has been scientifically examined for decades (Ferreira, 1965; Sontag, 1941; Van den Bergh et al., 2005). This substantial body of research has established that infants of mothers distressed during the prenatal period are at an increased risk for later neurological disorders (primarily cerebral palsy) and various cognition, attention, and language deficits (Brand & Brennan, 2009; Buitelaar, 2003; King & LaPlante, 2005). These children also exhibit a number of behavioral problems such as conduct disorder and ADHD, have poor growth attainment, and suffer a variety of health problems including respiratory infections and ear infections later in life (Hack, Klein, & Glover, 1995; Mulder et al.,

2002). Specifically, O'Conner and colleagues (2003) found that children of distressed mothers were more likely to have lower mental and motor development at eight months of age, lower mental development at two years and higher levels of behavioral and emotional problems at six years of age than those of non-distressed mothers. The associations between the mental health status of an expecting mother and infant outcomes are substantial, which leads one to speculate that these characteristics likely originated *in utero* and perhaps can be detected prenatally, which could allow for early detection and intervention.

Historically, obvious limitations have impeded the measuring and observation of fetal behavior; however, today the advancement of ultrasound imaging technology in obstetrics non-invasively provides us with a picture, both figuratively and literally, of fetal life inside of the womb. Although methods of in utero assessments are relatively new and ever evolving, the notion that a woman's emotional or psychological state can influence the in utero environment is not a new one (Sontag & Wallace, 1934). In fact, the idea that maternal emotional factors may play a role in fetal life is ancient and has been expressed in almost all known cultural settings (Dieter, Emory, Johnson, & Raynor, 2008; Ferreira, 1965). However, exploring how maternal psychological functioning affects fetal well-being, and subsequently the newborn, is a relatively new endeavor amongst researchers and is attracting increasing attention. As early as in 1867, heightened levels of fetal movement were observed in mothers experiencing severe emotional stress (Ferreira, 1965). More recent explorations have broadened. At present, a growing body of research amongst obstetricians, psychiatrists, and other health care providers suggests that maternal depression and other negative mood states, such as stress and anxiety, affect the expectant mother and her developing fetus (Corde et al, 2010; Kinsella & Monk, 2009). Recent studies of fetal heart rate [FHR] and fetal movement [FM] have focused on maternal distress

during pregnancy and its impact on fetal responsivity (Araki et al., 2010; DiPietro, 2010; Field et al., 2004; Kinsella & Monk, 2009). Given that perinatal morbidity and mortality are associated with FM and FHR (Bocking, 2003), studies linking these variables to outcomes have increased.

Although much of modern scientific inquiry focuses on the effects of maternal distress on childhood outcomes, underlying mechanisms, and psychological factors that might explain these outcomes, there is a notable gap in the literature identifying prenatal indicators (e.g. fetal responses) of those at risk for adverse post-natal outcomes. Investigating the association between fetal responsivity in distressed mothers and post-natal outcomes could prove to be an informative and beneficial exploration. Understanding more about the potential impact of maternal distress on fetal responsivity and consequently post-natal outcomes is of particular interest given the possible debilitating effects of the distress for the mother, potential life-threatening outcomes for the fetus, and long-term impact on the developing infant. A more comprehensive understanding of the impact of maternal distress on the unborn child and developing infant may lead to increased knowledge regarding the etiology and clinical presentation of both maternal distress and fetal responsivity, and may ultimately help target prevention and intervention efforts geared towards producing optimal birth and neurobehavioral outcomes.

Prenatal Distress

Stress & Pregnancy

Unfortunately, it appears that pregnancy and stress often go hand-in-hand for many women. Aside from worrying about the actual labor and safety of their unborn child, many pregnant women also worry about the financial aspects of pregnancy, about self-efficacy regarding caring for a child, and about social support. While some stress during pregnancy is to

be expected, and may even beneficial in terms of fetal maturation, high levels of stress can be dangerous for the fetus (DiPietro, 2006; Schneider, Moore, & Roberts, 2001; Van de Berg, 2005). Stress is an ambiguous term and a variety of broad and narrow definitions have been suggested within the fields of psychology, behavioral sciences, and physiology (Hogue, Hoffman, & Hatch, 2001). One definition provided by Levine (2000) broadly suggests that stress is any event that induces an increased secretion of glucocorticoids, whereas McEwen (2003) restricts the term as referring to events that are threatening to an individual and elicit physiological and/or behavioral responses. Conceptualizing antenatal stress is unique in that it affects both the mother and developing fetus. Specifically, the mother's hormonal stress response is physiologically transferred to the fetus through the altered intrauterine environment (Kinsella & Monk, 2009; Van den Bergh et al., 2005). When broadly defined, prenatal maternal stress has been linked to a variety of adverse reproductive events beginning during pregnancy (e.g. compromised fetal behavior and growth, maternal preeclampsia, and gestational diabetes) and extending through labor and delivery (e.g. unplanned cesareans, low birth weight, early gestational age) and the postpartum period (e.g. maternal mental health, infant temperament) (Saunders, 2006).

Animal Studies of Prenatal Stress

With respect to the prenatal period, the observation of maternal stress adversely affecting the development, behavior, and growth of the developing fetus has not been limited to only humans. Although this proposed study focuses exclusively on the human fetus, it is noted that seminal ground breaking studies with rodents and primates have lent much to our knowledge about the intrauterine environment and provided invaluable knowledge about fetal health and well-being. Many early studies examined the prenatal maternal stress construct using animal

models in which researchers were able to experimentally manipulate the stress exposure of pregnant animals through various methods of stress induction and precise control over the stress exposure (Pleuss et al., 2010; Weinstock, 2001; Welberg & Secki, 2001). Rhesus monkeys are sometimes used in psychology as animal models of prenatal stress, given that they are phylogenetically close to humans and similar in their central nervous system handling and regulation of stress (Schneider et al., 1999; Wu et al., 1995). However, pregnant rats are also frequently utilized due to their commercial availability, minimal cost, short gestation period, and large litters (Fujita, Ueki, Miyoshi, & Watanabe, 2010). Researchers have varied their methods for assessing the effects of prenatal stress in animals. In some studies, pregnant rhesus monkeys are subjected to random, loud noise bursts in a dark room (Coe et al., 2003), injections of stress hormones (Schneider et al, 2001), forced immobilization (Maccari, et al. 1995; 2007), immersion in cold water or exposure to heat or electric shocks (Weinstock, 2001). Despite the precise method used for stress induction, the results are relatively similar in outcome and corroborate human studies suggesting that gestational stress has an impact on fetal ontogeny. As in human studies, animal models suggest that beyond genetic factors, environmental prenatal events act on the developing fetus and can be important determinants of poor functioning as an infant (Glover, 2002; Gould, 1998).

Human Studies of Prenatal Stress

Animal studies do not provide a perfect analogue for determining the effects of prenatal maternal stress on human pregnancy. Although it is not ethical to experimentally expose pregnant women to varying degrees of stress throughout pregnancy, some investigators have utilized naturally occurring stressors (e.g. natural disasters) as an exemplar of stress during pregnancy. A number of studies have examined fetal and infant outcomes as a result of natural

disasters such as hurricanes (Zahran, Snodograss, Peek, & Weiler, 2010), ice storms (LaPlante, 2005), earthquakes (Glynn et al., 2001), and events such as the attacks on the World Trade Center (Yehuda et al., 2005). These studies have indicated that the effects of these stressors can be significant increases or decreases fetal movement (based on gestational age) and/or significantly lower gestational age and/or gestational weight at birth.

In addition to examining the effects of natural occurring stressors on fetal responsivity, cognitive challenges (e.g., Stroop Color-Word Test and mental arithmetic) have also been used to induce relatively short-lived stress in pregnant women. In one study, pregnant women who participated in a Stroop task at 24 and 36 weeks of pregnancy were found to have fetuses with increased FHR and reduced motor activity during the task (DiPietro, Costigan, & Gurewitsch; 2003). In a similarly designed study, maternal and fetal stress responses to either the Stroop Color-Word Test or a mental arithmetic task were measured; the fetuses of women with high anxiety showed an increase in FHR in response to the stressor compared to those of women with low anxiety (Monk et al., 2000). The tasks utilized in these studies elicited stress responses of increased cortisol levels and heart rate in the women and resembled mild cognitive stressors that these women likely encounter in the everyday course of pregnancy. Results of these psychophysiological studies thus suggest that prenatal maternal distress, as measured concurrently with fetal responsivity, has an impact on the developing fetus.

The great majority of human studies of the effects of maternal distress on the fetus have not, however, employed experimental stress inductions. Rather, these studies typically have obtained the women's self-reports of stress, conceptualized in a variety of ways (e.g. life events, perceived stress, state anxiety), and used these reports to predict an array of mother and fetal outcomes. For example, DiPietro, Hilton, Hawkins, Costigan, and Pressman (2002) investigated

the effects of stress, pregnancy-related hassles, and non pregnancy-specific daily stressors on FHR and FM at various points during pregnancy. The results indicated that women who reported higher levels of stress had more active fetuses; however, there were no consistent findings with respect to fetal heart rate.

Depression and Anxiety during Pregnancy

The contribution of maternal depression and anxiety to adverse fetal outcomes is increasingly becoming a major area of interest in a number of disciplines, especially psychology. Often, antenatal depression and anxiety are not recognized or treated given the symptoms shared between them and normal pregnancy changes (see Appendix A). An expecting mother's tiredness, problems sleeping, stronger emotional reactions, and changes in body weight and appetite are all common during pregnancy, but they could also reflect signs of distress. Data released by the National Institute of Mental Health [NIMH], (2001) revealed that more than 18 million adults experience a depressive disorder, including major depression annually. Similarly, approximately 14 million experience an anxiety disorder (NIMH, 2001). Furthermore, data from the National Comorbidity Survey concluded that roughly half of these adults are co-morbidly depressed and anxious (Kessler et al., 2008). Research on depression and anxiety has shown that both depression and anxiety are approximately twice as prevalent globally in women, compared to men, and the highest rates of both are seen during the childbearing years of the lifecycle (World Health Organization [WHO], 2008). These numbers alone conservatively estimate that about 800,000 mothers in the United States suffer from some form of depression and/or anxiety annually (CDC, 2008) and therefore highlight the importance of investigating the effects these disorders have on the unborn child.

Fetal Responsivity & Maternal Distress

There appears to be an early consensus emerging from the obstetric literature that maternal distress during pregnancy is associated with numerous adverse behavioral, developmental, social, and emotional infant and child outcomes (Brand & Brennan, 2009). However, evidence as to the exact nature of the association between maternal distress, fetal responses, and post-natal outcomes is still budding. As research on the prevalence of emotional distress and mental illness during pregnancy increases, research examining the effects of prenatal psychological distress on fetal responsivity (i.e. well-being) and birth outcomes will continue to emerge. Several recent studies suggest that antenatal depression and anxiety are significantly related to compromised fetal outcomes of growth, weight, heart rate, and movement. For example, a recent study by Hoffman and Hatch (2000) observed reduced growth of fetuses of mothers with elevated depressive symptoms, an outcome that has been linked in subsequent literatures to reduced infant alertness (Henrichs et al., 2009). More recently, Corde and colleagues (2010) reported that maternal anxiety and depression are both significant risk factors for a decrease in fetal growth. Similarly, Diego et al. (2006) found that self-reported symptoms of depression and anxiety were significantly negatively related to indices of fetal growth and fetal weight. Likewise, studies by Maina (2008), Sable and Wilkinson (2000), and Khashan and colleagues (2009) all suggest that mothers reporting high levels of depression and/or anxiety are at risk for fetuses of lower birth weights. Results of these psychophysiological studies highlight the importance of the fetal investigations and suggest that prenatal maternal anxiety and depression have a significant impact on the developing fetus, which can be revealed by concurrent measurement of fetal behaviors.

Fetal Responsivity Behaviors

Long before the introduction of ultrasonography in obstetrics, the developing fetus was an organism of interest to fetal behavior pioneers such as Forbes and Forbes (1927), Preyer (1890), Ray (1932), Sontag and Wallace (1935), and Spelt (1948). Today, it is well established that fetal responsivity is a reflection of fetal health and adaptation, as well as the maturity and integrity of the developing autonomic nervous system (Allister, Lester, Carr & Liu, 2001; DiPietro et al., 2000; Kinsella & Monk, 2009). As more knowledge is gained about the behavior of the fetus and factors that influence its development, opportunities are presented to enhance the health of the fetus and inform the treatment of the prenatal period. Fetal movement (FM) and fetal heart rate (FHR) are two of the most commonly investigated and important aspects of fetal behavior (Roodenburg et al., 1991), and thus are the responses explored in this study. Both FM and FHR are obstetrically assessed with a fetal actocardiotocograph, which provides an output of baseline heart rate and accelerations and decelerations due to stimuli and/or stress as well as data regarding the amplitude and frequency of fetal movement over a given amount of time. Therefore, observing abnormal FHR and/or FM responses could potentially help to determine if a fetus is at an increased risk for intrauterine death and/or compromised postnatal well-being.

Fetal Heart Rate. Fetal heart activity is easy to detect and measure and thus is the most commonly used measure of fetal distress. Normal fetal heart rate values range between 120 and 160 beats per minute (BPM) and are a signal of fetal fitness, indicating that the fetus is well supplied with both oxygen and nutrients (Farley & Dudley, 2009). A significant increase (tachycardia) or decrease (bradycardia) in FHR typically signals fetal jeopardy and increased chance of a miscarriage. Increased FHR results in increased energy utilization and could signal reduced blood flow to the fetus, blocked electrical signals within the heart, or uteroplacental

insufficiency in which there is a problem in the exchange between the uterus and placenta (Farley & Dudley, 2009). Similarly, a decrease in FHR is also a cause for alarm as it is perhaps indicative of too little oxygen supply to the tissues of the fetus (hypoxia), severe anemia, increased vagal tone, or potential congenital cardiac abnormalities (Farley & Dudley, 2009). Relatedly, fetuses have been found to have reduced fetal heart rate variability (DiPietro et al., 1996). Despite the abundance of research on fetal distress and FHR, there is still no clear definition or set of guidelines for measurement interpretation. A number of studies examine FHR at baseline, while others examine accelerations, decelerations, and variability. Standardized guidelines for the interpretation of the FHR have been suggested by the National Institute of Child Health and Human Development [NICHD]; however, recent attempts to develop a rigorously unambiguous definition for FHR distress have all been unsuccessful (Listron, Sawchuck, & Young, 2007; NICHD, 1997).

Whereas much is known about fetal heart rate as a biological proxy for fetal well-being, less is known about its response to maternal psychopathology. Not only are reports on the influence of maternal psychopathology on FHR scarce, they are also based on relatively small sample sizes, conducted by a homogenous group of researchers utilizing varied methods of assessment, and often reporting conflicting findings. Whereas Monk and colleagues (2004) found increased mean FHR in mothers who were depressed in response to a stressful cognitive task, Dieter and colleagues (2008) found a decrease in mean FHR in similar mothers in response to vibratory stimulation. Whether such effects can lead to a lasting impact on postnatal outcomes has not been conclusively shown.

Fetal Movement. Fetal movement (FM) is thought to be an index of fetal well-being and a valuable source of information in monitoring the neurological development of the fetus and in

assessing fetal health (Flenady et al., 2009). Fetal movement is the oldest and most commonly used method for assessing fetal well-being as it is also one of the few markers of fetal well-being that can be both assessed by the expecting mother and detected by the analysis of ultrasound images. In fact, maternal perception of fetal movements, during self screenings, remains commonly one of the first indicators of fetal well-being and has routinely become an important part of antenatal care (Froen et al., 2008). Fetal monitoring via assessing fetal movement, which encompasses duration, amplitude, and frequency of fetal movement in a given time, has been shown to be a useful indicator of distress, thereby indirectly reducing fetal mortality, indicating the possibility of promising outcomes for fetal movement screening as a part of prenatal care (Froen et al., 2008). A reduction in FM has been found to be associated with fetal hypoxia (reduction of oxygen supply to tissues), which is the third leading cause of fetal mortality (Bang, Bang, Baitule, & Reddy, 2005). A decrease in FM has also been found to correlate with congenital abnormalities, such as damage to the central nervous system, late development, growth inhibition, a reduction in adaptive capabilities of the fetus, and an increased incidence of stillbirth (Flenady et al., 2009; Heazel & Froen, 2008). In 1995, a team of researchers led by Groome found that fetuses of anxious mothers moved less than those whose mother was not anxious. Similarly, Dieter and colleagues (2008) observed that fetuses of depressed and anxious mothers moved less during vibratory stimulation. While a reduction of fetal movement is commonly seen in distressed mothers, the clinical significance of this difference, with regard to post-natal outcomes, remains unclear.

Overall, the findings of fetal responsivity studies with distressed, expecting mothers demonstrate the immediate effects of maternal distress on fetal development and offer insight into the potentially lasting impact of maternal mood during pregnancy. As highlighted by

DiPietro and colleagues (2000), there is significant continuity between fetal and infant neurobehaviors, suggesting that maternal distress during pregnancy not only influences the neurodevelopment of the fetus, but also impacts outcomes during infancy. Therefore, the early examination of maternal psychological and fetal physiological states may offer insight into the neurodevelopmental processes that unfold throughout childhood. This idea, that a mother's psychological state may have strong and long-lasting effects on the development of the child across a lifetime, supports the fetal origins hypothesis, which will be discussed in the proceeding section.

Etiologic Framework of Maternal Distress & Fetal Responsivity

Evaluating maternal distress and its influence on the fetal outcomes of heart rate and movement is warranted, as these measures are sensitive indicators of normal fetal developmental and non-optimal perinatal environment factors, perhaps indicative of adverse birth and neurobehavioral outcomes. The recent association between maternal psychological well-being during pregnancy and fetal welfare has not only attracted increasing attention (Araki et al., 2010; DiPietro, 2010; Field, 2003; Glover et al., 1999, Lundy et al., 1999), but has also supported the application of a hypothesis of fetal programming (Ellison, 2010). This hypothesis, which guides this study, focuses on the ability of alterations to the *in utero* environment, including maternal psychological state based alterations, to hinder the development of and possibility permanently affect the developing fetus (Ellison, 2010; Kinsella & Monk, 2009; Van den Bergh et al., 2005). According to this framework, these environmental alterations impact fetal well-being and have the potential to affect birth and neurobehavioral outcomes and highlight the role of maternal mental illness in determining pregnancy outcomes.

The Fetal Programming Hypothesis

The fetal programming hypothesis posits that conditions during pregnancy affect health later in life (Barker, 1990). The term "fetal programming" was coined by researcher David Barker to describe his findings from epidemiological studies that linked health problems in adults with low birth weight. It can be inferred from Barker's (1990, 1998, 2002) research that prenatal stress, depression, and/or anxiety result in changes in the fetal environment and thus affect the manner in which the fetus develops (Nathanielsz, 1999). In a recent review, Weerth, Buitelaar, and Mudler (2005) argue that the presence of prenatal distress affects the fetus specifically by leading to higher levels of the stress-related hormone, cortisol, which may affect how the baby responds to stress as a child and as an adult - thereby creating additional challenges and problems. As the framework for this potential study, the fetal programming hypothesis highlights the fact that significant maternal distress results in the secretion of corticotrophin-releasing hormone (CRH), a master stress hormone that triggers the release of glucocorticoid stress hormones such as cortisol, which results in the body shifting into crisis mode (Diego et al., 2006; Monk et al., 2004; Power & Shulkin, 2006). According to this view, the altered hormonal profile of the mother, due to her distress, creates an unfavorable fetal environment and essential physiological processes responsible for digestion, growth, and repair are shut down. Such a phenomenon could potentially explain numerous fetal outcomes, such as low birth weight, and preterm delivery (Nathanielsz, 2009; Stowe, Hostetter, & Newport, 2005) and contribute to the etiological explanation of the influence of maternal stress, anxiety, and depression on fetal heart rate and movement and post-natal outcomes.

Post-natal Outcomes

The desire to explore the beginnings of human life and to obtain a picture of human development and behavior as it emerges is not novel (Sontag & Richards, 1938). Recent technologic advances, however, provide a view inside the womb and allow for a more complete picture of prenatal development and post-natal outcomes. Fetal development occurs in the context of the maternal environment. Recent studies highlighting the effects of a mother's emotional state on the in utero environment and developing fetus, combined with the emergence of fetal programming hypotheses, support the premise of the current study examining the possible presence of prenatal precursors to less optimal birth and neurobehavioral outcomes.

Birth Outcomes

Adverse birth outcomes such as low birth weight, pre-term delivery, and intra-uterine growth retardation are recognized as important determinants of mortality in infancy and poor health outcomes occurring over the entire course of life (Barker, 1995). Birth outcomes, which are observed immediately at delivery, such as gestational age, low birth weight, and Apgar scores have immediate implications in terms of adverse, life threatening perinatal outcomes and non-life threatening outcomes that affect subsequent health throughout a lifetime.

Gestational Age. According to the Centers for Disease Control [CDC] (2011), a normal pregnancy lasts about 37-42 weeks, with preterm labor defined as labor that begins before 37 weeks of pregnancy. Approximately 12% of babies in the United States are born preterm, which is the primary cause of newborn complications and infant death before the age of one (CDC, 2011). In fact, in 2006, more than two-thirds of infants who died in the United States were born preterm (CDC, 2011). Whereas it is difficult to predict who will deliver preterm, obstetrical conditions and other factors such as psychological distress have been found to increase a

woman's risk for preterm delivery (Maina, 2008). Stress has been found to trigger a complex cascade of hormones inside the pregnant woman's body, which in return signals the fetus to leave the womb and results in the experience of uterine contractions (Glover & O'Conner, 2002; Van den Bergh, 2005). Therefore this study examined the relationship between fetal responsivity and gestational age (preterm delivery) among distressed mothers.

Birth weight. Low birth weight is often used as a proxy for adverse events to which the fetus was exposed to during development (Shi et al., 2004). The relationship between maternal prenatal distress and low birth weight babies has been robustly supported in the literature (Saunders, 2006), with studies frequently yielding results supporting the conclusion that mothers with high levels of distress have infants with low birth weights (Corde et al., 2010; Henrichs et al., 2009; Khashan et al., 2009; Maina, 2008; Sable & Wilkerson, 2000). Compared to infants of normal weight, low birth weight babies are at an increased risk for negative circumstances such as perinatal morbidity, infections, impaired learning abilities, and delayed motor and social development (CDC, 2012). Given this, this study explored the relationship between fetal movement and heart rate as possible early indicators of an infant at risk for low birth weight.

Apgar Score. For more than 50 years, an Apgar score has been used as a quick assessment of newborn health immediately after birth. The test, done 1 and 5 minutes after delivery, allows for health care providers to access the neonate's survival potential by examining it's (A)ppearance or skin color, (P)ulse, (G)rimace or response to stimulation, (A)ctivity or muscle tone, and (R)respiration (Haddad & Green, 2011) (see Appendix B). The test at 1 minute post delivery indicates how well the baby tolerated the birthing process, with the 5 minute score reflecting how well the baby is adapting to life outside of the womb. The 5 minute score, compared to the 1 minute, has come to be regarded as the better predictor of infant survival

(Casey, McIntire, & Leveno, 2001; Finster & Wood, 2005). Some studies have examined Apgar scores as a predictor of neurological development but not without criticism, for the score was created for the purpose of predicting neonatal health and survival chances (Casey, McIntire, & Leveno, 2001; Gonzales & Salirrosas, 2005; Finster & Wood, 2005). This study examined the ability of fetal responsivity variables to serve as precursors to poor Apgar scores, an exploration absent in the current literature.

Neurobehavioral Outcomes

Neonatal Behavioral Assessment Scale [NBAS]. A growing interest in the early identification of developmental problems gave rise to the Neonatal Behavioral Assessment Scale in 1973, a measure that provides a descriptive, qualitative picture of an infant's neurological and behavioral responses to their environment up to two months old (Beal, 1986; Brazelton & Nugent, 1995) (see Appendix C). Thereafter, in addition to gestational age and birth weight, some researchers began reporting a significant relationship between prenatal stress and neurobehavioral postnatal outcomes. Specifically, in 2003 Field and colleagues reported that newborns of anxious mothers spent more time in deep sleep and less time in quiet and active alert states and showed more state changes and poor performances on the NBAS, indicating less than optimal motor maturity and autonomic stability. Similarly, an earlier study by Lou et al. (1994) found that infants exposed to high levels of antenatal stress scored lower on neurodevelopmental assessments. The NBAS, which consists of 28 behavioral and 18 reflex items, assesses the baby's capabilities across different developmental areas (autonomic, motor, state and social-interactive systems) and provides information about the baby's strengths, adaptive responses, and possible vulnerabilities (Picciolini, Gianni, Fumagalli, & Mosca, 2006). This study investigated if fetal heart rate and movement responses correlate with infant

performance on the NBAS and if so, how and which of the three empirically derived clusters of alertness, reflexes, and self-regulation (Emory, Walker, & Cruz, 1982) produces the strongest link. As a new area of exploration, results of this study could inform early detection and intervention efforts for infants at risk of less than optimal development.

Study Purpose & Rationale

The primary purpose of this study was to extend the literature examining the relationship between maternal distress and adverse post-natal outcomes to include fetal responses of heart rate and movement as possible precursors of compromised development and early indicators of the need for intervention. Overall, the current state of the literature suggests that prenatal maternal distress is associated with a host of adverse birth and neurobehavioral outcomes including preterm labor, lower birth weight, higher fetal heart rate, less movement, and cognitive, attentional, and motor deficits of the infant. To my knowledge, no study has examined the relationship between maternal distress and adverse post-natal outcomes, with fetal responses of heart rate and movement as possible precursors to such results. Taking advantage of the established relationship between maternal distress measures completed during pregnancy and fetal responses and compromised post-natal outcomes, this study attempted to identify, prior to delivery, fetuses at an increased risk for adverse post-natal outcomes, which might become useful indicators of a need for early intervention. Additionally, this study aimed to investigate factors, such as infant gender and severity of maternal distress (a composite score of BDI, BAI, and PSS measures), which could moderate the relationship between fetal responses and post-natal outcomes. For example, conflicting reports as to whether male and female fetuses differ in their response to maternal distress and performance on post-natal assessments can be found throughout the literature (Hernandez-Martinez, 2010; Patchev & Almeida, 1998; Robles de

Medina et al., 2003). Similarly, varying degrees of distress have been found to yield contrasting fetal and infant responses (DiPietro, Costigan, & Gurewitsch; 2003; Glynn et al., 2001; LaPlante, 2005; Yehuda et al., 2005; Zahran, Snodograss, Peek, & Weiler, 2010). Lastly, time of assessment (e.g., 2nd trimester vs. 3rd trimester) was also explored as a possible moderator. Substantial evidence from developmental studies suggests that with advancing gestation, fetal heart rate decelerates and fetal movement increases, indicating that the fetal response may vary according to the time of assessment (i.e. trimester differences) (Sorokin et al., 1982). However, there is empirical evidence contradicting this postulate with fetuses of distressed mothers (Allister, Lester, & Carr, 2001). Conflicting findings, such as elevated FHR even late in the third trimester (a time when it is expected to decrease) suggest that a better understanding of fetal responses, with respect to trimesters, in predicting post-natal outcomes is needed (Heazell & Froen, 2008; Sadovsky, 1977). Early trimesters (i.e. second compared to third trimester) have been reported to be particularly sensitive to the long-term effects of antenatal distress (Khashan et al., 2008; Van den Berg et al., 2005). Are certain fetal responses worse (i.e. more likely to result in negative outcomes) depending on the trimester? Perhaps variability in the strength of the relationship based on trimesters may provide information regarding periods of sensitivity in which the fetus is more vulnerable and at an increased risk of poor post-natal outcomes. A better understanding of the relationship between maternal distress and adverse post-natal outcomes and possible fetal predictors and confounds would facilitate the development of preventative measures that might help the expecting mother and reduce her child's risk for adverse developmental outcomes.

Rationale

There are two broad classes of fetal responses that are accessible, non-invasive, and helpful

to the behavioral scientist with a developmental interest. These include a broad range of physiologic indices such as fetal heart rate and movement. These fetal responses include measures of overt behavior in terms of frequency, amplitude and duration. Individually or in combination these responses provide information about the integrity of fetal systems critical for life and are relevant as the foundation for behavioral development. With strong support for the link between maternal distress and adverse post-natal outcomes, it is worth exploring the power of fetal responses to predict fetuses at an increased risk for less than optimal birth and neurobehavioral outcomes and potentially subsequent developmental problems. Inherent in the mass of information relevant to fetal development is the challenge of selecting the most relevant variables for behavioral research, especially considering recent technologic advances. This selection should be based on a variable's underlying relevance for adaptation to environmental challenges and information from previous empirical studies that provide direction in this regard.

As such, fetal heart rate was chosen because of its sensitivity to overall physiologic homeostasis and perfusion of vital organ systems (e.g., heart, lungs and brain) necessary for life. Cardiac muscle is unique and once the heart begins to beat in the first trimester of gestation it normally does not stop until death many decades later. Heart rate variability is regulated by parasympathetic inputs and modulates cardiac responses to cognitive and other mental challenges. As such, heart rate is implicated as a feature of higher order mental processes and lower level homeostatic processes that regulate energy utilization and functional adaptation. FHR is highly reactive to metabolic needs (oxygen availability) and basic cognitive processing (orienting response, habituation and dishabituation) so it serves as a good barometer of overall functional integrity at a time when traditional dependent measures of behavioral and cognitive function are inappropriate (e.g., during pregnancy). Moreover, its sensitivity to vascular

impairments that affect neurological integrity and mental function make it an excellent predictor and status variable for many bio-behavioral paradigms in psychology. The rationale adopted in this dissertation is that FHR is a sensitive assay of stress reactivity, integrity of the autonomic nervous system (ANS), and individual difference in temperament and environmental challenges requiring mental effort. Therefore, for practical and scientific reasons FHR was chosen as one of the central predictor variables in this research.

In contrast to FHR, fetal movement (FM) is a central component of the motor system and can be viewed as an output system reflecting endogenous and exogenous challenges. Endogenous challenges require coordinated movement responses, repetitive motor responses and postural adjustments that facilitate homeostatic regulation. Emory and Isrealian (1998) in reviewing the early work of Preyer (1882;1885) and later that of Gottlieb, (1973) explored the fundamental problem of *psychogenesis* and eventually asserted the "motor primacy theory" that organisms are *active* before they are *reactive*. Thus, the earliest movements stem exclusively from processes in the central nervous system and may therefore be instructive where questions focus upon the relation between early movement responses and later neurobehavioral and higher cortical mental processes. Moreover, FM and FHR show some rather predictable and consistent relationships in non-compromised fetuses and infants. For example, coupling of movement and heart rate during late gestation is a reassuring sign that the developing autonomic and motor systems are being integrated and under central nervous system control. In addition, the direction of change in FHR is also predicted by fetal movement (tachycardia) and any deviation from this pattern is a sign of fetal risk for later cardiovascular or other developmental problems. These examples are only a few of the important physiologic properties of FHR and FM that allow them to be used in early studies of infant development, prenatal stress and neurological compromise.

Thus, examining fetal variables that include heart rate and movement, in combination with maternal distress, as the basis for predicting newborn well-being and autonomic regulation, attention, and motor control is an exploration missing in the current literature but one that could have several far reaching effects.

Hypotheses

The preceding review of the Fetal Programming Hypothesis (Barker, 1990) and empirical evidence in the area of maternal distress, fetal responses, and post-natal outcomes suggested the following hypotheses:

Hypothesis 1. Fetal responsivity variables of heart rate and movement will serve as significant, strong predictors of birth outcomes of prematurity/gestational age, birth weight, and Apgar scores independently. This hypothesis is based primarily on the findings of Corde et al. (2010), Diego et al. (2006), and Maina (2008).

Hypothesis 2. Fetal responsivity variables of heart rate and movement will serve as significant, strong predictors of neurobehavioral outcomes on the NBAS, most specifically on the clusters of alertness, self-regulation, and reactivity. This hypothesis is based primarily on the findings of Field and colleagues (2003).

Hypothesis 3. The relationship between fetal responses and post-natal outcomes will be moderated by fetal sex and severity of distress. Specifically, the fetal responses of female fetuses will yield weaker predictions of adverse post-natal outcomes compared to those of male fetuses. This hypothesis is based primarily on the findings of Hernandez-Martinez and colleagues (2010). Similarly, mothers experiencing higher levels of distress will have stronger fetal responses predicting adverse outcomes, compared to mothers experiencing lower levels of distress.

Method

Overview

The data for this study were collected as part of a larger NIH funded parent study (1 RO1 MH64732-01, Dr. Eugene Emory – Principal Investigator), "*Studies in Behavioral Perinatology-Fetal Activity in Maternal Psychopathology,"* conducted to investigate the psycho-obstetrical aspects of maternal mental illness as they relate to fetal and infant neurobehavioral organization. The 152 women represented by the data were recruited from the Psychiatry Obstetrics Consultation/Liaison (Psych/OB) Service at Grady Memorial Hospital in Atlanta, Georgia after being formally diagnosed (by psychiatrists and clinical psychologists with the aid of the SCID) with Major Depressive Disorder (Single Episode or Recurrent, Without Psychotic Features) (DSM-IV-TR, American Psychiatric Association, 2000). Women who were between the ages of 18-45 and the gestational age of their fetus at recruitment was less than 25 weeks, as determined by ultrasound examination, were eligible to participate in this study. The patients at the clinic are approximately 70% African-American, 20% Hispanic, and 10% Caucasian. The sample distribution is very representative of the typical population at a large county hospital in the Southeastern United States. All participants were paid $25.00 per visit for a total of four visits (see Figure 1). The demographic composition of the Psych/OB and standard OB Service patients is comparable. Pregnant women were eligible to participate if they had no medical condition other than their psychiatric diagnosis. While the targeted adult population was pregnant women, the sex of the fetuses was not considered.

Inclusion/Exclusion. Women were specifically excluded from participation if: a) they were carrying more than one fetus; b) they smoke, drank alcohol or used illicit drugs; c) the fetus had shown any serious abnormalities on ultrasound exam; d) the pregnancy was complicated

(e.g., maternal diabetes, hypertension, placenta previa); e) the gender of the fetus was unknown at recruitment; f) the mother had been prescribed medication other than prenatal vitamins or antidepressants medication that may affect the fetus; or g) the mother did not plan to deliver at Grady Memorial Hospital.

Participants

Participant (N = 152) characteristics are presented in Table 1. The majority of the women enrolled in the study were African American (83.2%), single (79.1%) and at least a high school graduate (56.3%). Participants ranged in age from 15 to 42 years old (M = 22.6 years, SD = 5.4 years). Over half of the participants were unemployed (51.8%), primiparous (i.e. women having their first live birth) (51.3%), and with an annual household income of less than $10,000 (51.5%). The effect size of maternal distress on fetal responsivity observed in the Beckwith & Emory (n.d.) study was small (d = .37). Utilizing this effect size a power analysis indicated that 1 - b > .95 (a = .05, two-tailed) with 42 participants per group (Erdfelder, Faul, & Buchner, 1996).

Recruitment. All recruitment took place at Grady Memorial Hospital on either the Psych/OB or standard OB service. Once potential participants had been identified, they were informed of the study and asked if they wished to participate. The Co-PI, Dr. Dieter, who served as on-site director, recruited potential participants with the assistance of a female research associate. It was likely that a referring psychiatrist or OB physician was present during the initial stage of each recruitment. Recruitment entailed describing the general goals of the study, the psychometric assessments, and the salvia and urine sampling procedures. The degree of commitment expected from each participant was explained and coordinated with the Psych/OB and OB services. Each mother was informed that she would receive $25.00 per visit. Both Drs.

Emory and Dieter have succeeded in recruiting women with this strategy during previous pilot studies.

Procedure

After recruitment and eligibility screening, each mother was telephoned and reminded of her appointment several days prior to her visit. She was also mailed a reminder. The first visit occurred between the 26th and 28th weeks gestation, thus reflecting relatively early development; the second visit occurred between 32 and 34 weeks gestation, thus reflecting relative fetal maturity, and the third visit occurred anytime after 35 weeks gestation, which reduced attrition due to premature birth. A post-partum assessment occurred approximately one month after delivery. At each visit, each mother was administered various psychometric instruments (see below), a salvia sample was taken, fetal/infant assessment conducted, and she then received payment for participation.

Visit 1: *26-28 weeks***.** The details of the study were explained to the participant and women who agreed to participate signed the informed consent, provided demographic information, and completed maternal psychiatric assessments consisting of the Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1997), Beck Anxiety Inventory (BAI; Beck, 1990), and Perceived Stress Scale (PSS; Cohen et al., 1983). Upon completion of the maternal assessments, the mother was asked to provide a salivary cortisol sample and take a urinary drug screen prior to the start of the fetal monitoring session. Each fetal monitoring session began by asking the mother about any significant changes that might influence her pregnancy or if any medical complications had developed. The mother was then escorted to the examination room for the fetal heart rate and movement examination. At least one research assistant was a woman

and present during the entire examination. Twenty minutes after fetal monitoring the mother was asked to provide another saliva sample and received payment for participation.

Visit 2: *32-34 weeks***.** The procedure for the second visit was almost parallel to that of the first. The women were asked to complete the BDI-II, BAI, and PSS and to report any new developments or complications, since their last visit, that might have an impact on her pregnancy. Urinary drug screens and salivary cortisol samples were taken prior to the start of the fetal monitoring session. Another salivary cortisol sample was taken 20 minutes after completion of the fetal assessment and the participant received $25.00 for her participation.

Visit 3: *≥35 weeks.* Daily contact with the Maternal/Fetal Unit was made to ensure notice of delivery and research assistants rotated weekends to ensure delivery and first postpartum day data collection. Post-delivery assessments were conducted within 24 hours of birth. The exact time when the neonate was assessed depended on whether he/she resided in the newborn nursery or the mother's hospital room, as those residing in the nursery allowed for easier access and earlier evaluation. The post-delivery evaluation consisted of documenting obstetrical and postnatal complications, measuring maternal psychiatric symptoms with the BDI-II, BAI, and PSS, and gathering maternal saliva samples to measure cortisol and obtaining a urine sample for drug screening, as well as obtaining a newborn salivary cortisol sample pre and post administration of the NBAS.

Visit 4: *One month postpartum.* Near the end of the first postnatal month, mothers were reminded of their upcoming one-month postpartum examination by both a telephone call and letter. Mother and infant were be evaluated by separate RAs to ensure "blinded" observations. During the one-month visit the NBAS was re-administered and pre- and post-NBAS salivary sample was collected from the infant. Similarly, the mother completed BDI-II, BAI, and PSS

measures again, followed by salvia and urine sample collections. She then received payment for her participation.

Measures

Maternal Distress Measures During Pregnancy

The Beck Depression Inventory-II (BDI-II). (BDI-II; Beck, Steer & Brown 1997) The BDI consists of 21 items scored on a four-point scale (0 to 3). Items address the presence or absence and severity of physical symptoms, behaviors, thoughts, and feelings associated with depression that the participant may have experienced in the last two weeks. The highest score for each of the twenty-one questions is three, therefore the highest possible total for the whole test would be sixty-three (see Appendix D).

The Beck Anxiety Inventory (BAI). (BAI; Beck, 1990) The BAI consists of 21 items scored on a four-point (0 to 3) scale. Items address the presence or absence and severity of physical symptoms, behaviors, thoughts, and feelings associated with anxiety that the mother may have experienced in the last week. The BAI is scored on the same scale as the BDI and therefore lends itself more easily to a comparison of the severity of anxious to depressive symptoms than would another psychometric measure that uses a different scale. The highest score for each of the twenty-one questions is three, thus the highest possible total for the test is sixty-three (see Appendix E).

The Perceived Stress Scale (PSS). (Cohen et al. 1983) The PSS is a 10-item instrument that is used to assess the degree to which mothers perceive their lives as burdensome, uncontrollable, and unpredictable. The PSS does not inquire about actual stressful events, but instead asks persons to rate their perception of events as stressful and their perceived ability to handle stress. Each item is responded to on a five-point scale ranging from “never” to “very

often". PSS scores are obtained by reversing responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1 & 4 = 0) to the four positively stated items (items 4, 5, 7, & 8) and then summing across all scale items. This measure is scored by adding all 10 items together. The minimum score is 0, and the maximum score is 40. Higher scores indicate a high level of stress (see Appendix F).

Prenatal Outcomes/Fetal Responses

Fetal movement and fetal heart rate are assessed with a fetal actocardiotocograph, which provides an output of baseline heart rate and accelerations and decelerations due to stimuli and/or stress. Additionally, the actocardiotocograph outputs data regarding the amplitude and frequency of fetal movement over a given amount of time.

Fetal Heart Rate. For this study, the variables from the FHR composite included: *Mean Baseline FHR* at Times 1 and 2 and Mean *Post-stimulation FHR* at Time 1 and 2. The *Mean Baseline FHR* was score achieved by recording the FHR for 10 minutes during each prenatal assessment in the absence of any external stimulation. Similarly, the *Mean Post-stimulation FHR* score was measured during a 10 minute window post-stimulation by a Toitu Fetal Stimulator (TR-30, HAH Medical, Lone Tree, CO), a device that delivers a mild vibratory sensation to the mother's abdomen with minimal acoustic stimulation. These measures are selected because they capture resting cardiovascular tone and reactivity to stimulatory challenges. In addition, in a general sense, increases in FHR following external stimulation predict more positive outcomes than decreases following stimulation.

Fetal Movement. In the behavioral domain, neural maturation and control over motor systems is indexed by the duration and frequency of fetal movement in the baseline condition and in response of external stimulation. In general, the longer the duration of fetal movement the more mature the behavioral system appears to be. The reason for this phenomenon is predicated

on the control of isolated muscles compared to coordinated movement of large muscle groups. Thus, the movement variables of greatest interest in this study will center around maturational profiles in the behavioral domain. They include the mean time spent moving (within a 10 minute window) in both pre and post stimulation conditions: *Mean Baseline Fetal Movement* at Time 1 and 2 and *Mean Stimulation Total Fetal Movement* at Time 1 and 2.

Postnatal Outcomes

Birth Outcomes

Gestational Age and Birth weight. Outcomes of gestational age (weeks) and birth weight (grams) were obtained from hospital medical records documented at birth.

Apgar. The five infant characteristics of (A)ppearance or skin color, (P)ulse, (G)rimace or response to stimulation, (A)ctivity or muscle tone, and (R)respiration (Haddad & Green, 2011) (see Appendix B) are assessed and assigned a score from 0-2. The total score (max = 10) is the sum of the 5 components, with a score of 7 or higher being indicative of an infant in good to excellent health. The test at 5 minutes postpartum reflects how well the baby is adapting to life outside of the womb. The 5 minute score, compared to the 1 minute, has come to be regarded as the better predictor of infant survival (Casey, McIntire, & Leveno, 2001; Finster & Wood, 2005). The 5 minute Apgar score was recorded from the hospital medical records of the participants.

Neurobehavioral Outcomes

Neonatal Behavioral Assessment Scale [NBAS]. The Scale, which consists of 28 behavioral and 18 reflex items, assesses the baby's capabilities across different developmental areas (autonomic, motor, state and social-interactive systems) and provides insight with regard to the baby’s strengths, adaptive responses, and possible vulnerabilities (Picciolini, Gianni, Fumagalli, & Mosca, 2006). Given the number of NBAS subscales and desire to prevent Type I

or Type II error in this study select subscales were used. The three behavior factor composites derived from stepwise multiple regression analyses of fetal responses predicted 3 empirically derived neurobehavioral dimensions of alertness, self-regulation, and reflexes, which were used in this study (Emory, Walker, & Cruz, 1982).

Results

Sociodemographic Descriptive Statistics

Statistical Analyses

All statistical analyses were performed using SPSS for Windows version 19.0 statistical software. The α level of the study was .05 with one-tailed *p*-values calculated for all directional hypotheses The one sample Kolmogorov-Smirnov test (K-S test) was used to test the assumption of normal distribution for continuous variables. Residual scores from regression analyses were examined for assumptions of normal distribution and equal variance.

As is the case with most longitudinal studies, not all women who completed questionnaires or provided fetal data at Time 1 completed questionnaires or gave fetal data at Time 2. Causes of attrition were primarily due to unforeseen circumstances (e.g., administration error, equipment malfunctioning, and transportation or dual scheduling conflicts). Missing data rates varied from 13.0% to 55.5% (See Tables 3 and 4 for the valid cases of study variables). Since the number of missing cases was very high for many variables, imputation was not an appropriate strategy for replacing missing data. Instead, availability-case analysis was adopted for each of the statistical inquiries in order to optimize the power of each analysis.

Overall Sample

Participant (N = 152) characteristics are presented in Table 1. The majority of the women enrolled in the study were African American (83.2%), single (79.1%) and earned at least

a high school diploma (56.3%). Participants ranged in age from 15 to 42 years old (M = 22.6 years, SD = 5.4 years). Over half of the participants were unemployed (51.8%). Most were primiparous (51.3%). This study did not warrant controlling for confounds typically found in the literature (e.g., alcohol and drug use) as these women were excluded from study participation.

Women were asked to report on their health during pregnancy. The majority of participants reported an uncomplicated pregnancy (96.2%). The most commonly reported medical conditions during the current pregnancy were hypertension (2.1%) and anemia (1.4%). Additionally, the majority of participants (83.6%) reported the pregnancy as unplanned.

Descriptive Statistics

Maternal Distress. Table 2 contains the means and standard deviations for self-report maternal distress data (e.g. depression, anxiety, and stress) at Times 1 and 2. In general, women in our sample reported relatively mild levels of maternal depression, anxiety, and stress.

Birth Outcomes. Descriptive statistics for birth outcomes are presented in Table 3. The newborns of the women in this study were almost equally divided between males and females with the majority being males (53%) and generally healthy based on standard birth weight and gestational duration standards. The majority of the women (85%) gave birth to normal birth weight babies (i.e. >2500 grams) and 26.8% experienced preterm delivery (i.e. prior to 37 weeks gestation). Similarly, the majority of the babies (94%) received APGAR scores of 8 or better at 5 minutes post birth.

Infant Outcomes. Descriptive statistics for infant outcomes on the NBAS are presented in Table 4. The infants of the women in this study varied on neurobehavioral functioning clusters of alertness, reflex, and self-regulation at Time 1, with average scores of 5.6, 4.9, and 5.0

respectively. Although similar in alertness at Time 2 (M = 5.8), the infants of this study were functioning at lower levels on clusters of reflex (M = 4.5) and self-regulation (M = 3.6).

Data Exploration and Transformations

Birth Outcomes. Analyses revealed violations of test assumptions for each of the birth outcome dependent variables. In an attempt to correct for these violations of assumptions, the variables of *Birth Weight, Gestational Age, and Apgar 5 min* were transformed. The square root transformation was applied to *Gestational Age.* The natural logarithmic function corrected the non-normality of *Birth Weight*. The majority of mothers gave birth to babies assigned a 9 on the post-birth Apgar examination. Consequently, *Apgar 5 min* scores were recoded into categorical variables to allow for logistic regression. Participant scores were dichotomized and dummy coded as 0 or 1 depending on whether they scored optimally (i.e. Apgar score of 9) or non-optimally (i.e. Apgar score of 0-8) on the test at 5 minutes after birth.

Visual inspection of the scatterplots of birth outcome residuals regressed against the predicted value (Y') revealed relatively equal scatter both above and below the perfect predictability line and across the range of the x-axis. There was small scatter outside of the 95% confidence interval in each of the plots, but this scatter seemed to be comparatively equal. Similarly, P-P plots were created where the standardized regression residuals were plotted against the cumulative portion expected if the sample were a normal distribution and yielded points that were clustered nicely around the straight line for *Gestational Age*. This indicated that the samples were from normal distributions. The P-P plot for *Birth Weight* continued to indicate mild positive skew following the transformation. The natural logarithmic transformation, however, substantially reduced the deviation of the residuals from the line thereby reducing the non-normality of residuals.

Infant Outcomes. Analyses also revealed significant violations of assumptions for infant outcome variables. *NBAS_AlertT1, NBAS_AlertT2, NBAS_ReflexT1,* and *NBAS_RegulationT1* were successfully transformed with the square root function. The violations of assumptions for *NBAS_ReflexT2* and *NBAS_RegulationT2* were substantially reduced with the squared function.

Study Hypotheses

Fetal Responsivity and Birth Outcomes. The first hypothesis that fetal responsivity variables of heart rate and movement would serve as significant, strong predictors of birth outcomes of gestational age, birth weight, and Apgar scores was tested using separate linear and logistic regression analyses.

Fetal Heart Rate and Birth Outcomes. Regression analyses revealed that fetal responses of heart rate – mean baseline FHR at Time 1, mean baseline FHR at Time 2, mean stimulation HR at Time 1 and mean stimulation HR at Time 2 -- failed to explain a significant portion of l variance in and did not predict gestational age and birth weight outcomes (see Table 5). This finding did not support the association between fetal heart responses and birth outcomes of gestational age and weight.

Binary logistic regression analyses were conducted to predict Apgar scores at 5 minutes post delivery (1 = non optimal performance rendering a score less than 9, 0 = optimal performance, rendering Apgar test score of 9). Separate analyses were conducted for mean baseline FHR at Time 1, mean baseline FHR at Time 2, mean stimulation FHR at Time 1 and mean stimulation FHR at Time 2. The fetal heart rate responsivity variables failed to reliably distinguish between newborns with optimal and less than optimal Apgar scores at 5 minutes post delivery, mean baseline FHR at Time 1, χ^2 (1, N = 90) = 1.91, p = .33; mean baseline FHR at Time 2, χ^2 (1, N = 43) = .11, p = .74; mean stimulation FHR at Time 1, χ^2 (1, N = 62) = .13, p =

.72, and mean stimulation FHR at Time 2, χ^2 (1, N = 39) = .26, p = .32 (see Table 6). These findings fail to support an association between fetal responsivity variables of heart rate and Apgar scores at 5 minutes post delivery.

Fetal Movement and Birth Outcomes. Regression analyses revealed two trends between fetal movement and birth outcomes that failed to reach the alpha level (α = .05) set for this study (see Table 7). The data indicate that babies who had high levels of movement after stimulation at Time 2 tended to be born earlier than babies who did not move a lot post stimulation (p = .07). Similarly, babies who moved less at baseline for Time 1 tended to have lower birth weights (p = .10). Remaining fetal variables of movement – mean baseline FM at Time 2 and mean total movements after stimulation at Time 1 – failed to explain a significant portion of variance and did not predict gestational age and birth weight outcomes (p >.05) (see Table 6). These findings did not support the association between fetal movement responses and birth outcomes of gestational age and weight.

Binary logistic regression analyses were conducted to predict Apgar scores at 5 minutes post delivery (1 = non optimal performance rendering a score less than 9, 0 = optimal performance, rendering Apgar test score of 9). Separate analyses were conducted for mean baseline FM at Time 1, mean baseline FM at Time 2, mean stimulation FM at Time 1 and mean stimulation FM at Time 2 for a total of four analyses. Analyses were not statistically significant, indicating that the fetal movement responsivity variables were not reliably distinguishing between newborns with optimal and less than optimal Apgar scores at 5 minutes post delivery, mean baseline FM at Time 1, χ^2 (1, N = 62) = .71, p = .40; mean baseline FM at Time 2, χ^2 (1, N = 39) = .65, p = .42; mean stimulation FM at Time 1, χ^2 (1, N = 61) = .01, p = .97, and mean stimulation FM at Time 2, χ^2 (1, N = 38) = .19, p = .66 (see Table 6). These findings fail to

support an association between fetal responsivity variables of movement and Apgar scores at 5 minutes post delivery.

Fetal Responsivity and Infant Outcomes. The second hypothesis that fetal responsivity variables of heart rate and movement would serve as significant, strong predictors of neurobehavioral outcomes of alertness, self-regulation, and reactivity (i.e. abnormal reflexes) on the NBAS was explored using simple linear regression.

Fetal Heart Rate and Infant Outcomes. Bivariate regression analyses revealed no significant associations between mean baseline FHR at Time 1, mean baseline FHR at Time 2, mean stimulation FHR at Time 1 and mean stimulation FHR at Time 2 and neurobehavior alertness at Times 3 and 4, abnormal reflexes at Time 3, and ability to self regulate (i.e. self-consolability) at Time 4, (see Table 8). However, bivariate regression analyses revealed that mean baseline FHR at Time 1 was a significant predictor of abnormal infant reflexes at Time 4. Infants with a low baseline HR had a lower number of abnormal reflexes. A linear regression established that mean baseline FHR at Time 1 significantly predicted abnormal infant reflexes at Time 4, $F(1, 32) = 4.54$, $p = .04$ and low baseline FHR at Time 1 accounted for 12.0% of the explained variability in abnormal infant reflexes (see Table 8). Similarly, regression analyses revealed that mean baseline FHR at Time 1 also significantly predicted self-regulation behavior at Time 3. Infants with higher baseline FHR had lower self-regulation scores on the NBAS. Linear regression analyses established that mean baseline FHR at Time 1 significantly predicted self-regulation behavior at Time 3, $F(1, 32) = 5.33$, $p = .02$ and baseline FHR at Time 1 and accounted for 14.0% of the explained variability in infant self-regulatory behaviors (see Table 8).

Fetal Movement and Infant Outcomes. Bivariate regression analyses were conducted to examine the ability of fetal movement variables – mean baseline FM at Times 1 and 2 and mean

FM post stimulation at Times 1 and 2 – to predict infant outcomes of alertness, abnormal reflexes, and ability to self-regulate on the NBAS. Analyses revealed that the various aspects of fetal movement examined were not significant predictors of infant outcomes on the NBAS (see Table 9).

Moderator Analyses. The third hypothesis of this study examined the ability of fetal sex and distress severity to moderate the relationship between fetal responses and post-natal outcomes. Fetal sex and distress severity were proposed as significant moderators of this relationship. To examine 'distress severity,' a principal component analysis was conducted and used to create a weighted linear composite of BDI, BAI, and PSS scores. As suggested by Preacher and Hayes (2004), regression analyses were used to test the hypothesized moderation effects. Specifically, the SPSS macro PROCESS procedure written by Hayes (2012), Model 1 (see Figure 2), which uses the general linear model to estimate effects in interaction models, was used in analyses. This model involved one independent variable, one dependent variable, and one moderating variable, moderating the path between the independent and dependent variables. For this study, separate analyses were conducted for each dependent variable. Given our small sample size, the recommended 10,000 bootstrapped resamples were used to estimate the 95% bias corrected and accelerated confidence intervals (Preacher & Hayes, 2004).

The results of the moderator analyses revealed that the relationship between baseline FHR at Time 1 and abnormal fetal reflexes at Time 4 as well as self-regulation at Time 3 is significantly moderated by distress severity at Time 1. Analyses also revealed a trend of fetal gender moderating the relationship between baseline FHR at Time 1 and abnormal reflexes at Time 4. Specifically, results indicated that the relationship between baseline FHR at Time 1 and abnormal reflexes at Time 4 is moderated by the severity of distress at Time 1 [t (29) =2.34, p =

.02] and accounts for 29% of the variance [$F(3, 27) = 3.68$, $p = .02$]. Infants with low baseline FHR at Time 1 display fewer abnormal reflexes at Time 4 if the mother's stress level was also low. Similarly, the relationship between baseline FHR at Time 2 and self regulation at Time 3 was moderated by severity of distress at Time 1 [$t(28) = -2.26$, $p = .03$] and accounts for 24% of the variance [$F(3, 26) = 2.83$, $p = .05$]. At mild levels of stress, an increase in baseline FHR predicts an increase in self-regulating behaviors at Time 3. Lastly, a trend suggested that in the relationship between baseline FHR at Time 1 and abnormal reflexes at Time 4 [$F(3, 28) = 2.29$, $p = .09$], gender accounted for 19% of the variance. Male fetuses who had a high baseline FHR tended to have more abnormal reflexes [$t(30) = 2.56$, $p = .01$].

Discussion

The current state of the literature suggests that prenatal maternal distress, measured in a variety of ways, is associated with a host of adverse reproductive outcomes including labor and delivery complications, reductions in birth weight, and decreases in gestational age. Despite converging evidence from animal studies, analogue stress studies, and retrospective studies, many questions remain to be answered regarding the impact of maternal distress on post-natal outcomes. Additionally, one of the most pressing unresolved issues in the literature involves whether or not measurable indicators of fetal functioning can be identified that would predict less than optimal post-natal outcomes. The purpose of this study was to explore the ability of fetal responses to predict adverse birth and neurobehavioral outcomes and to address pertinent questions in the field regarding factors that may increase or decrease the impact of this relationship.

The predominately negative results of this study do not offer much support for the hypothesis that fetal responses are useful predictors of post-natal outcomes. Overall no

definitive statements can be made from the results of the analyses completed. While not the desired outcome, the lack of statistical significance does reveal important properties of these variables and can be instructive in the pursuit of the relationships hypothesized. Thus, the question becomes, why did this study not find a relationship in any measurable way that can be taken as support for the association between fetal responses and post-natal outcomes?

The role of the stimulus in assessments of fetal responsivity

The degree and nature of fetal responses to stimulation depends heavily on the potency of the stimulus, a notion that has been discussed for decades (DiPietro et al., 1996; Groome et al., 1993; Leader et al., 1984). A closer inspection of the stimulation procedures revealed that FHR and FM in response to vibratory stimulation may not be in the same class of stimulation as a uterine contraction in the antepartum or intra-partum period. In fact, vibratory stimulation to the fetus is not considered a significant stressor but a stimulus to which the organism may respond with FHR change or FM. While it does provide an assay of nervous system responsiveness, its value lies in how the response reflects more subtle aspects of cortical control and integrated responses at a higher level within the central nervous system. Vibratory and auditory stimulation are far better assays of nervous system integrity when they are used in paradigms that reflect learning and memory, not necessarily those that recruit self-regulatory and homeostatic mechanisms that ensure physical survival of the organism. Antepartum and intra-partum FHR reflect the robustness and physiological toughness of the autonomic and central nervous system to significant stress that can be life threatening. The fetus and infant's ability to mount a response to these challenges tells the investigator what the integrity of the system is at a fundamental biologic level. This level is the foundation for responses at higher levels within the nervous system. In other words, both the stimulus and the response used in this study are

different from those used in previous studies where a relationship between FHR, FM and infant outcome was found. For example, DiPietro et al. (2010) found that vibratory stimulation applied to the maternal abdomen, as in this study, was more likely to generate fetal startlings and abrupt state changes than intense heart rate and motor responses. Previous studies have consistently observed strong associations between maternal distress and postnatal outcomes when more challenging forms of stress are employed, such as labor stress (Dieter et al., 2001; Emory & Toomey, 1998; 1991). Data suggest that a fetus exposed to a chronically stressful intrauterine environment will show more compromise during the universal challenge of labor stress (i.e., uterine contractions) compared to those not subjected to such experience (Emory & Toomey, 1998). Based on the work of Emory and Noonan (1984) it can be concluded that under more potent stimuli, like labor stress, fetuses are more likely to exhibit impaired responses of fetal heart rate and movement, yield profiles indicative of exposure to a compromised uterine environment, and subsequently perform the poorest on post-natal assessments. For example, Emory and Toomey (1991) found that the extent to which the fetus exhibited recovery from uterine contractions (based on the return of FHR to baseline after decelerations) robustly predicted Apgar scores and NBAS performance post-natally. Given these findings, it is posited that using the intra-partum FHR and neonatal behavior relationship as an example, it is far easier to detect weakness or compromise in a system when it is confronted with a massive stressful challenge like that involved in the fetuses' response to uterine contractions. The fetuses' ability to meet this challenge, organize itself and regulate subsequent behavioral responses tell us a great deal about its biologic resilience, including autonomic reactivity and latency to recovery from stress. Fetal heart rate or movement responses to vibratory stimulation in a habituation paradigm would not be a good assay for biologic resilience, nor a predictor of latency to

recovery from stress. Thus, the nature of the questions posed in this aspect of the dissertation need to be revisited.

Across studies, the issue of operational definitions of distress has been highlighted. Variable measurement of distress has left the field with unanswered questions regarding the nature of the distress construct, whether particular dimensions of distress are stronger predictors of post-natal outcomes than others, and what are the best assessment tools to use with expecting women (Beckwith & Emory, n.d). Although the multidimensional approach to distress assessment is most popular (e.g., Dominguez et al., 2008; Glazier et al., 2008), in their 1993 prospective study, Wadhwa and colleagues found that pregnancy specific anxiety measures were most related to gestational age, whereas stress was more associated with birth weight. Along the same lines, Lobel and colleagues a year earlier found a main effect for perceived stress on birth weight and gestational age at delivery, compared to other measures. More recently, Roesch, Dunkel-Schetter, Woo, and Hobel (2004) found evidence that pregnancy-related stress, but not anxiety, was strongly associated with reduced gestational age. These findings led not only to the reviewing of the correlations of all variables, (see Table 10) but specifically the item content of the maternal self-report variables in the study, which included three questionnaire measures related to stress. While none of the instruments were powerful predictors of fetal/infant outcomes, in supplemental analyses, a noticeable difference was detected in two areas. First, it appears that the very limited results were stronger for the Perceived Stress Scale than for the Beck Depression and Beck Anxiety scales combined. (see Table 11) Thus, even though the findings were small and could have resulted by chance alone, the pattern reveals that the PSS is more highly correlated with fetal/infant responses. The reader is reminded that this interpretation is offered with full knowledge that the statistical findings are inconclusive. The questionnaires

all include self-report items endorsed by the mother. The BDI and BAI are primarily symptom oriented and ask questions of objective fact such as "has your appetite changed" or "do you have trouble sleeping". Answers to such questions are an indication of the possibility that the responder has symptoms related to either depression or anxiety, both of which are correlated with stressful experiences. In contrast, the PSS provides a more subjective set of responses that reflect the responders' perception of experience as stressful, thus controlling for the objective nature of the experience and whether it is related to clinical symptoms. An important caveat is contained in this rather subtle difference among these self-report measures. An individual's perception of experience is a far better measure of how they actually experience the phenomenon than a proxy measure that is more related to clinical symptoms that are not individually pathognomonic. In other words the threshold for experiencing events as stressful varies across individuals such that a specific event might be very stressful for one person and not at all stressful for another. Therefore, in a very fundamental way the PSS, which ignores the objective nature of an event in deference to its meaning to the observer, should correlate better with other variables that are presumed to be related to stress and in return tap specific aspects of stress that may be differentially related to adverse post-natal outcomes, which will be discussed more later in reviewing this study's findings.

Lastly, concerns about the specific variables chosen for this study may partly explain the negative findings for post-natal outcomes. Whereas consensus with regard to the assessment of neurobehavioral integrity of the fetus does not exist, most studies, including the present one, have examined fetal responses of heart rate and movement within the parameters of baseline and response to stimulation outputs. These variables, however, may not be ideal. Some researchers have postulated that differences in rate and variability are more reflective of nervous system

integrity and more subject to neural influences of maternal distress (Emory & Dieter, 2006), compared to baseline differences. Relatedly, DiPietro and colleagues (1996) found that infants experiencing high maternal stress also had reductions in fetal heart rate variability.

Thus, measurement of variability in heart rate, compared to baseline values, might prove more useful (Nijhuis et al., 2000; Suzuki et al., 2001) in the prediction of adverse post-natal outcomes. Similar to fetal heart rate variables, measures chosen to represent fetal movement are equally varied. Although movement counts, as employed with this study, are cost-effective and convenient for researchers, their usefulness in the context of fetal monitoring as an indication of distress may not be as useful as observing more complex movement patterns (Hof et al., 2002). With mothers who are distressed, observing variations in *defined* movements has been found to have more clinical significance than individual movements in terms of reflecting the developing nervous system (Hof et al., 2002; Kurjak et al., 2004; Velazquez and Rayburn, 2002). Thus, utilizing other variables might improve predictions of post-natal outcomes in future studies.

Study Findings

Having provided a critique of this study, and with the caveats about chance results in mind, it may be beneficial to provide a brief review of the study findings to inform future studies in this area. Overall, FHR at Time 1 appears to be useful in statistically predicting infant outcomes of alertness and self-regulation. On the other hand, trends were observed for FM and birth outcomes of gestational age and birth weight. None of the fetal responses were able to predict Apgar scores at 5 minutes. Within the limitations of the methods, small sample size, and unexpectedly healthy babies (e.g. optimal Apgar scores, gestational age, and birth weight) in this sample, the following conclusions can be drawn.

Predicting Post-natal Outcomes

Birth Outcomes. The assessment of FHR and its significance in predicting fetal well-being has received increased attention in recent years for its standardized ability to depict fetal well-being. Analysis of computer cardiotocographs has the theoretical advantage of providing a reproducible and objective interpretation of FHR by quantifying parameters that are difficult to assess by the human eye. In this study, FHR variables were not predictive of birth outcomes of gestational age, birth weight and Apgar scores, which challenges the hypothesis that mood-based alterations in the expecting woman's HPA-axis activity affect the fetus and impact neonatal outcomes. If fetal responses vary according to maternal distress, as a result of a compromised intrauterine environment which allows stress hormones to cross the placenta, thus reducing placental blood flow and evoking fetal hypoxia, then a decrease in birth weight and gestational age is justifiably expected (Dieter, Emory, Johnson, & Raynor, 2008). However, a closer examination of the literature revealed several reasons that might account for the discrepancies. First, in many studies it has been found that a reduction in FHR variability, as previously discussed, and not low baseline rates, is more indicative of fetal hypoxia and subsequently low birth weight and decreased gestational age (Druzin, 1989; George et al., 2004). Additionally, the vast majority of studies that have consistently demonstrated an association between prenatal distress and low birth weight have used predominately Caucasian samples (Arias et al., 2003) whereas the current study used an African-American sample. Whereas several studies found high baseline FHR in distressed pregnant women (Fink, 2010; Monk et al., 2000; Monk et al., 2004), the mean baseline FHR of the fetuses of our study was 145, and in the normal range. This, perhaps, is reflective of the low levels of distress reported by the women in our sample. Our women reported mild (versus moderate and severe) levels of depression, stress, and anxiety

and FHR predictability of adverse birth outcomes is more robust in samples of severely distressed women (Hilmert et al., 2008; Li, Liu, & Odouli, 2009; Monk et al., 2004; Orr, James, & Prince, 2002). Contradictory to numerous significant findings in the literature, several investigations do not support a direct association between distress and birth weight (St-Laurent, et al., 2008) or gestational age (Ruiz, et al., 2001) when lower levels of distress are present. Notably, a study on pregnant African American women also failed to indicate that birth weight and gestational age are predicted by distress levels (Dominguez, et al., 2005).

Contrary to FHR, trends were observed for select variables of FM in predicting birth outcomes of gestational age and birth weight. Fetuses who had fewer movements at Time 1 tended to have low birth weight. Similarly, fetuses who had high levels of movement after stimulation were tended to be of lower gestational age. Both outcomes are prenatal manifestations of abnormal psychophysiological reactions that resulted in adverse post-natal outcomes, potentially due to a compromised central nervous system. Relatedly, DiPietro et al. (1996) found the coupling of behavior in response to vibratory stimulation to be reflective of central nervous system maturity and integrity.

The Apgar score is the most commonly used measure of newborn infant well-being at delivery. Numerous studies have demonstrated the effectiveness of the Apgar test in the early detection of children with developmental delays and in need of intervention (Odd et. al., 2008). However most of these studies used retrospective data from birth records and examined at-risk populations where the births were complicated or problems were anticipated (Odd et al., 2008; Thorngren-Jerneck & Herbst, 2001). Additionally, the Apgar examination is semi-objective and open to interobserver variability and subject to measurement error, factors that could account for low power. Additionally, factors such as mode of delivery (e.g.,vaginal vs. caesarean) have been

found to affect Apgar scores, as caesarean sections are common in complicated pregnancies (Thorngren-Jerneck & Herbst, 2001). The mean Apgar score for the newborns in this study was 8.7 and approximately 70% were delivered vaginally, both of which are indicative of the infant's optimal health status and low likelihood of having poor outcomes.

Infant Outcomes. Contrary to birth outcome findings, cautious interpretation of the results of this study does suggest an association between prenatal behavior and infant behavior on the NBAS. Specifically, low baseline FHR at Time 1 significantly predicted infant outcomes of low frequency of abnormal reflexes and ability to self-regulate, clusters which are generally thought to reflect CNS maturity (DiPietro et al., 1996; Emory & Dieter, 2006). This finding has been supported in the literature as other studies have found that low FHR was predictive of poor NBAS performance (El-Dib, Massaro, Glass, & Aly, 2011). On a related note, the trends of this study suggest that the relationship between FHR at Time 1 and abnormal infant reflexes at Time 4 is moderated by severity of stress and gender, while self-regulation at Time 3 is moderated by the severity of distress. However, there are two unexpected findings, while inconclusive, that warrant further attention. They are the possible relationship between measures obtained at time T1 vs. T2 and the maternal self-report findings from the PSS.

In the first instance, it appears that any relationship using a time varying construct is strengthened when the outcome variable is linked to responses occurring around 26-28 (i.e. Time 1) weeks gestation. This raises the question as to why would this relationship be stronger since the interval between initial assessment and outcome is longer than if the assessment occured at 32-34 weeks gestation (i.e. Time 2). One interpretation, which is supported by previous research on infant viability and other studies of fetal maturation, is that the period around 26-28 weeks is by all accounts a neuro-motor-integrative (NMI) period (Emory & Israelian, 1998), which is a

time of rapid growth and maturation. The quality of the responses during this time period may reflect the degree in which the baby is developing. Specifically, the presence of fetal movement and heart rate coupling behaviors, which are observed around 26 weeks, is an early sign of the fetus is approaching a normative trajectory development (Baser, 1992; Dieter et al., 2008; DiPietro, 1996). In a relative sense, the period from 32-34 weeks is latent to that of the NMI period, meaning that the formation of autonomic-motor linkages, increases in parasympathetic tone and neural architecture at the cortical level are all in ascendency during NMI. At 32-34 weeks these systems are in place and rapid growth is proceeding. Neuro-motor-integration indexes a maturational epoch for the fetus, one that will feature considerable variation from one baby to the next. Given this wider variation in development occurring during NMI, outcomes that are linked to responses during that period are probably more indicative of variations among fetuses than responses obtain during the relatively latent period from 32-34 weeks.

An exploratory intercorrelation matrix of all variables yielded the second instance of interest. Although potentially spurious, the findings of this supplemental analysis revealed that the PSS measure was more highly correlated with post-natal outcomes than the BDI and BAI individually or collectively. As already alluded to in the previous section, maternal perception of stress is probably a more reliable assay of internal state than reliance on self-report of symptoms that are proxies for that state. Therefore, while none of the statistical findings are those that engender a strong or even modest conviction of the true relationship between maternal stress, fetal responses and birth outcomes, the limited findings and their pattern do suggest that a focus upon the NMI fetal period around 26-28 weeks and use of the Perceived Stress Scale may be promising avenues for future research.

Limitations and Future Directions

Although modest, the results of this study provide some suggestion that fetal response variables, measured differently and in a more distressed population, may be useful in predicting birth outcomes. However, several methodological limitations should be highlighted. Primarily, our small sample size limited power. A larger sample may be required to identify robust effects of fetal responsivity on post-natal outcomes. Moreover, recruiting from multiple hospitals to obtain a sample that is more diverse and representative of pregnant women may be necessary. It may also be the case that the association between maternal distress, fetal responses, and post-natal outcomes varies as a function of demographic characteristics, as has been reported by other researchers (Hilmert et al., 2008). A more diverse sample allows for the exploration of several other factors that may increase or decrease the association between maternal distress, fetal responses, and post-natal outcomes. The present study sample was relatively psychologically healthy, compared to those typically in the literature, experiencing mild (versus moderate or severe) levels of depression, stress and anxiety. Studies with more diverse samples using a more potent stress stimulus such as labor distress and employing measures of subjective distress might be more useful.

Although this study employed a longitudinal design, due to attrition not all women participated in both assessments. This missing data not only decreased power but may have reduced the representativeness of the remaining sample. Future studies with the same longitudinal nature should consider implementing appropriate strategies to decrease attrition rate. For example, emails and phone calls before each planned assessment time could be arranged to remind the participants.

Additionally, this study was a risk study and only explored factors that contributed to adverse post-natal outcomes. Another benefit to having a more representative sample is the ability to explore other key variables that may serve as protective factors, such as coping and social support. Perhaps a more informative exploration would be one in which the full spectrum of, as opposed to only adverse outcomes, is explored. Although many studies of prenatal stress are conducted to inform the larger goal of preventing clinically-relevant adverse outcomes, it is also important to determine how prenatal stress operates in pregnancies that result in full-term or normal weight infants. Ideally studies would identify fetal responses that predict a range of developmental dysfunction as well as resilience.

Despite the primarily negative findings, this study points to the need for continued research on maternal distress, fetal responses, and post-natal outcomes. It has been long accepted that the neurobehavioral functioning assessed at birth reflects the prenatal environment, and this study highlights the importance of finding reliable ways to identify women during pregnancy whose infants are at risk for adverse post-natal outcomes.

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Tables and Figures

Table 1

Participant Characteristics (N=152)

Participant Characteristics	**M(SD)**
Age	22.6 (5.3)
Participant Characteristics	**%**
African American	83.2%
Hispanic	13.7%
Caucasian	1.1%
Asian	0.5%
Other	1.5%
Single	79.1%
Married	6.1%
Separated	1.4%
Partnered	13.4%
Annual Income Under $10K	51.5%
Annual Income Between $10K-19K	25.4%
Annual Income Between 20K-40K	23.1%
High School Graduate	56.3%
College Graduate	3.5%
Some College	19.1%
GED	13.2%
No Diploma	30.5%
Employed	48.2%
Unemployed	51.8%
Unplanned Pregnancy	83.6%
Planned Pregnancy	16.4%
First Child	51.3%
Second Child	36.9%
Third Child	5.9%
Fourth Child	3.9%
Fifth or more	2.0%

Table 2

Means, Standard Deviations, and Stability of Maternal Distress across Time

	Time 1 Subset (N=152)		Time 2 Subset (N=117)	
	M	**SD**	**M**	**SD**
BDI-II (0-63)	15.8	7.3	13.8	6.8
BAI (0-63)	12.5	9.1	11.9	8.5
PSS (0-40)	19.5	10.2	14.1	12.6

Note: Possible ranges of each instrument are shown in parentheses.

Table 3

Descriptive Statistics – Birth Outcomes at Time 3

Birth Characteristics	**%**
Gender (N=152)	
Male	52.8
Female	47.2

Birth Characteristics	**N**	**M**	**SD**
Birth weight (g)	138	3059.2	613.4
5-min Apgar (0-10)	134	8.7	.91
Gestational Age (weeks)	142	38.4	2.4

Note: Score ranges and measurement units are shown in parentheses.

Table 4

Descriptive Characteristics – Infant Outcomes

	Time 3 Subset			Time 4 Subset		
	N	**M**	**SD**	**N**	**M**	**SD**
Infant Characteristics						
NBAS: Alert Cluster (1-9)	70	5.6	1.3	63	5.8	1.4
NBAS: Reflex Cluster (1-9)	73	4.9	2.6	61	4.5	2.6
NBAS: Self-Regulation (1-9)	71	5.0	2.3	66	3.6	1.9

Note: Score ranges are shown in parentheses

Table 5

Simple Regression Analyses: Fetal Heart Rate Responses on Birth Outcomes

Model Criterion	**Predictors**	**R**	**R^2**	**F**	**B**	**t**	***p*-Value**
Gestational Age	Mean Baseline FHR_T1	.19	.04	1.07	.01	1.03	.31
	Mean Baseline FHR_T2	.34	.12	1.83	.03	1.56	.12
	Mean Stimulation FHR_T1	.13	.02	.47	.02	.69	.49
	Mean Stimulation FHR_T2	.16	.03	.32	.02	.43	.67
Birth Weight	Mean Baseline FHR_T1	.14	.02	1.31	-9.75	-1.15	.25
	Mean Baseline FHR_T2	.08	.01	.24	-1.87	-.49	.63
	Mean Stimulation FHR_T1	.12	.01	.37	24.37	.61	.55
	Mean Stimulation FHR_T2	.31	.10	1.27	15.26	1.47	.16

* = p <.05; ** = p < .01. a = marginally significant $p \leq .10$.

Table 6

Logistic Regression of Fetal Responsivity Variables Predicting Non-optimal Apgar Scores at 5min

Predictor	**B**	**Wald χ^2**	**Block χ^2**	**Model χ^2**	***p***	***N***
Fetal Heart Rate Variables						
Mean Baseline FHR_T1	0.03	0.94	0.91	0.91	0.33	90
Mean Baseline FHR_T2	0.02	0.27	0.11	0.11	0.74	43
Mean Stimulation FHR_T1	- 0.05	0.12	0.13	0.13	0.72	62
Mean Stimulation FHR_T2	- 0.21	0.97	0.26	0.26	0.32	39
Fetal Movement Variables						
Mean Baseline FM_T1	- 2.29	0.76	0.71	0.71	0.40	62
Mean Baseline FM_T2	- 1.69	5.27	0.65	0.65	0.42	39
Mean Stimulation FM_T1	- 0.01	0.01	0.01	0.01	0.97	61
Mean Stimulation FM_T2	0.03	1.10	0.19	0.19	0.66	38

* = p <.05; ** = p < .01. a = marginally significant p $\leq$ .10.

Table 7

Simple Regression Analyses: Fetal Movement Responses on Birth Outcomes

Model Criterion	**Predictors**	**R**	**R^2**	**F**	**B**	**t**	***p*-Value**
Gestational Age	Mean Baseline FM_T1	0.09	0.00	0.25	-0.02	-.51	.62
	Mean Baseline FM_T2	0.18	0.03	0.48	-0.04	-.84	.41
	Mean Stimulation FM_T1	0.05	0.00	0.59	-0.01	-0.24	.81
	Mean Stimulation FM_T2	0.36	0.13	1.83	-0.04	-1.88	**.07**[#]
Birth Weight	Mean Baseline FM_T1	0.31	0.09	2.82	50.78	1.68	**.10**[#]
	Mean Baseline FM_T2	0.32	0.08	1.44	15.26	0.37	.71
	Mean Stimulation FM_T1	0.16	-0.01	0.68	-15.7	-.82	.44
	Mean Stimulation FM_T2	0.17	-0.05	0.32	6.05	.23	.82

#$p<.10$

Table 8

Simple Regression Analyses: Fetal Heart Rate Responses on Infant Outcomes

Criterion	Predictors	R	R^2	F	B	t	*p*
NBAS_Alert_T3	Mean Baseline FHR_T1	0.06	0.00	0.09	0.00	0.30	0.77
	Mean Baseline FHR_T2	0.09	0.00	0.01	0.04	0.03	0.97
	Mean Stimulation FHR_T1	0.21	0.04	1.18	-0.15	-1.08	0.29
	Mean Stimulation FHR_T2	0.00	0.00	0.00	-0.00	-0.02	0.98
NBAS_Alert T4	Mean Baseline FHR_T1	0.27	0.07	2.26	-0.26	-1.50	0.14
	Mean Baseline FHR_T2	0.01	0.00	0.01	0.02	0.03	0.97
	Mean Stimulation FHR_T1	0.19	0.04	1.00	-0.11	-1.00	0.32
	Mean Stimulation FHR_T2	0.11	0.12	0.22	-0.06	-0.46	0.65
NBAS_Reflex_T3	Mean Baseline FHR_T1	0.11	0.12	0.42	-0.03	-0.64	0.52
	Mean Baseline FHR_T2	0.15	0.02	0.78	-0.13	-0.89	0.38
	Mean Stimulation FHR_T1	0.12	0.02	0.23	0.04	0.80	0.27
	Mean Stimulation e FHR_T2	0.17	0.30	0.55	0.22	0.75	0.46
NBAS_Reflex_T4	Mean Baseline FHR_T1	0.35	0.12	4.54	0.09	2.13	**0.04***
	Mean Baseline FHR_T2	0.34	0.11	4.17	0.35	2.04	0.50
	Mean Stimulation FHR_T1	0.06	0.00	0.10	0.10	0.41	0.31
	Mean Stimulation FHR_T2	0.08	0.00	0.13	0.10	0.37	0.72
NBAS_SelfRegul_T3	Mean Baseline FHR_T1	0.38	0.14	5.33	-0.08	-2.31	**0.02***
	Mean Baseline FHR_T2	0.24	0.11	4.13	-0.14	0.12	0.67
	Mean Stimulation FHR_T1	0.08	0.00	0.19	-0.06	-0.44	0.66
	Mean Stimulation FHR_T2	0.30	0.09	1.58	0.35	1.25	0.23
NBAS_SelfRegul_T4	Mean Baseline FHR_T1	0.02	0.00	0.02	0.04	0.13	0.89
	Mean Baseline FHR_T2	0.01	0.00	0.01	0.03	0.21	0.73
	Mean Stimulation FHR_T1	0.00	0.00	0.00	0.00	0.04	0.97
	Mean Stimulation FHR_T2	0.19	0.04	0.69	-0.10	-0.83	0.41

* = p <.05; ** = p < .01. a = marginally significant p ≤ .10.

Table 9

Simple Regression Analyses: Fetal Movement Responses on Infant Outcomes

Criterion	Predictors	R	R^2	F	B	t	*p*-Value
NBAS_Alert_T3	Mean Baseline FM_T1	0.28	0.08	2.23	-0.19	-1.48	0.15
	Mean Baseline FM_T2	0.31	0.09	1.64	0.23	1.28	0.22
	Mean StimTotal FM_T1	0.02	0.00	0.01	-0.01	-0.11	0.91
	Mean StimTotal FM_T2	0.04	0.00	0.03	-0.03	-0.17	0.87
NBAS_Alert T4	Mean Baseline FM_T1	0.32	0.10	3.37	-0.19	-1.84	0.18
	Mean Baseline FM_T2	0.15	0.02	0.38	0.09	0.62	0.54
	Mean Stimulation FM_T1	0.10	0.01	0.30	-0.05	-0.54	0.58
	Mean Stimulation FM_T2	0.04	0.00	0.03	-0.02	-0.18	0.86
NBAS_Reflex_T3	Mean Baseline FM_T1	0.22	0.05	1.67	0.26	1.29	0.21
	Mean Baseline FM_T2	0.09	0.00	0.15	-0.11	-0.39	0.70
	Mean Stimulation FM_T1	0.11	0.12	0.41	0.12	0.64	0.53
	Mean Stimulation FM_T2	0.02	0.00	0.08	-0.02	-0.09	0.93
NBAS_Reflex_T4	Mean Baseline FM_T1	0.07	0.00	0.17	0.09	0.42	0.68
	Mean Baseline FM_T2	0.08	0.00	0.12	-0.09	-0.35	0.73
	Mean Stimulation FM_T1	0.07	0.00	0.18	-0.09	-0.43	0.67
	Mean Stimulation FM_T2	0.23	0.05	1.09	0.22	1.04	0.31
NBAS_SelfRegul_T3	Mean Baseline FM_T1	0.04	0.00	0.05	-0.05	-0.24	0.81
	Mean Baseline FM_T2	0.03	0.00	0.02	0.04	0.13	0.89
	Mean Stimulation FM_T1	0.02	0.00	0.01	0.02	0.13	0.90
	Mean Stimulation FM_T2	0.03	0.00	0.01	0.03	0.12	0.91
NBAS_SelfRegul_T4	Mean Baseline FM_T1	0.09	0.00	0.25	0.07	0.50	0.61
	Mean Baseline FM_T2	0.04	0.00	0.03	0.04	0.17	0.87
	Mean Stimulation FM_T1	0.06	0.00	0.14	0.05	0.38	0.71
	Mean Stimulation FM_T2	0.18	0.03	0.65	-0.11	-0.80	0.43

Table 10

Correlations: All Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Fetal Measures																	
1. Mean BFHR T1	___	.743**	.317**	.212	.017	-.309	-.073	-.204	-.138	-.217	-.171	.059	-.269	-.111	.353*	-.378	.022
2. Mean BFHR T2	.743**	___	.082	.141	.159	-.102	.157	-.142	-.062	-.340	.148	.009	-.364	.021	-.160	-.313	.499*
3. Mean SFHR T1	.317**	.082	___	.115	.314**	-.145	.143	.094	.066	-.037	.077	-.209	-.186	-.154	.344*	-.078	.006
4. Mean SFHR T2	.212	.141	.115	___	.122	.045	.369	.193	.162	-.143	.120	-.006	-.112	.173	.085	.309	-.188
5. Mean BFM T1	.017	.159	.314**	.122	___	.061	.535**	.147	.170	.242*	.185	-.281	-.323	.220	.074	-.042	.087
6. Mean BFM T2	-.309	-.102	-.145	.045	.061	___	.327	.356*	.209	.195	.094	.314	.149	-.091	-.079	.033	.039
7. Mean SFM T1	-.073	.157	.143	.369	.535**	.327	___	.515**	.098	.107	.050	-.142	-.183	.233	.029	.030	.051
8. Mean SFM T2	-.204	-.142	.094	.193	.147	.356*	.515**	___	.356*	.287	-.037	-.477	-.268	.215	-.043	.255	-.213
Birth Outcomes																	
9. Birth Wt	-.138	-.062	.066	.162	.170	.203	.098	.356*	___	.600**	.249**	-.288*	.010	-.147	.016	.103	.097
10. Gest. Age	-.217	-.340*	-.037	-.143	.242*	.195	.107	.287	.600**	___	.118	-.261	.040	-.107	-.236*	.054	.165
11. 5min Apgar	-.171	.148	.077	.120	.185	.094	.050	-.037	.249**	.117	___	-.065	-.147	.131	-.097	.066	-.180
Infant Outcomes																	
12. NBAS Alert T1	.059	.009	-.209	-.006	-.281	.314	-.142	-.477	-.288*	-.261	-.065	___	.220	-.299*	.114	.089	-.051
13. NBAS Alert T2	-.269	-.364	-.186	-.112	-.323	.149	-.183	-.268	.010	.040	-.147	.22	___	-.251	-.025	.306*	.058
14. NBAS Reflex T1	-.111	.021	-.154	.173	.220	-.091	.233	.215	-.147	-.107	.131	-.299*	-.251	___	.125	-.093	.020
15. NBAS Reflex T2	.353*	-.160	.344*	.085	.074	-.079	.029	-.043	.016	-.236*	-.097	.114	-.025	.125	___	.022	-.131
16. NBAS Self-reg T1	-.378*	-.313	-.078	.309	-.042	.033	.030	.255	.103	.054	.066	.089	.306*	-.093	.022	___	-.078
17. NBAS Self-reg T2	.022	.499*	.006	-.188	.087	.039	.051	-.213	.097	.165	-.180	-.051	.058	.020	-.131	-.078	___

* = p <.05; ** = p < .01; BFHR=Baseline Fetal Heart Rate, SFHR=Post-Stimulation Fetal Heart Rate, BFM=Baseline Fetal Movement, SFM=Post-Stimulation Fetal Movement, NBAS=Neonatal Brazelton Assessment Scale, T1=Time 1, T2=Time2.

Table 11

Intercorrelations between Measures of Distress and Infant/Fetal Outcomes

		PSS_T1	PSS_T2	BDI_T1	BDI_T2	BAI_T1	BAI_T2
1.	Birth weight	-.091	-.092	.116	.042	.039	.006
2.	Gestational Age	.081	.020	.113	.158	.095	.097
3.	Apgar 5 Minutes	.045	-.015	.014	.114	-.001	.051
4.	Mean Baseline FHR_T1	-.102	-.227	-.109	.031	-.101	-.019
5.	Mean Baseline FHR_T2	-.086	-.034	-.124	-078	.173	-.113
6.	Mean Stimulation FHR_T1	**-.246***	-.215	.027	.148	-.143	.113
7.	Mean Stimulation FHR_T2	**.032***	.070	-.172	-.064	-.045	.129
8.	Mean Baseline FM_T1	-.091	.082	-.130	-.189	.131	.007
9.	Mean Baseline FM_T2	-.005	-.098	.124	.053	**.301***	.053
10.	Mean Stimulation FM_T1	-.009	.002	-.044	-.139	.281	.135
11.	Mean Stimulation FM_T2	**-.322***	-.027	-.094	.006	.194	.144
12.	NBAS Alert_T3	-.082	-.122	-.114	-.020	-.147	-.030
13.	NBAS Alert_T4	**-.273***	**-.310***	-.078	-.206	-.093	-.211
14.	NBAS Self-Regulation_T3	-.131	.254	-.002	.094	.181	.042
15.	NBAS Self-Regulation_T4	-.079	-.119	-.086	.002	-.040	.035
16.	NBAS Abnormal Reflex_T3	.012	.**277***	.023	-.068	.069	-.071
17.	NBAS Abnormal Reflex_T4	-.112	-.155	-.035	.013	.002	.006

* = p <.05; PSS=Perceived Stress Scale, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory, NBAS=Neonatal Brazelton Assessment Scale, FM=Fetal Movement, FHR=Fetal Heart Rate, T1=Time 1, T2=Time2

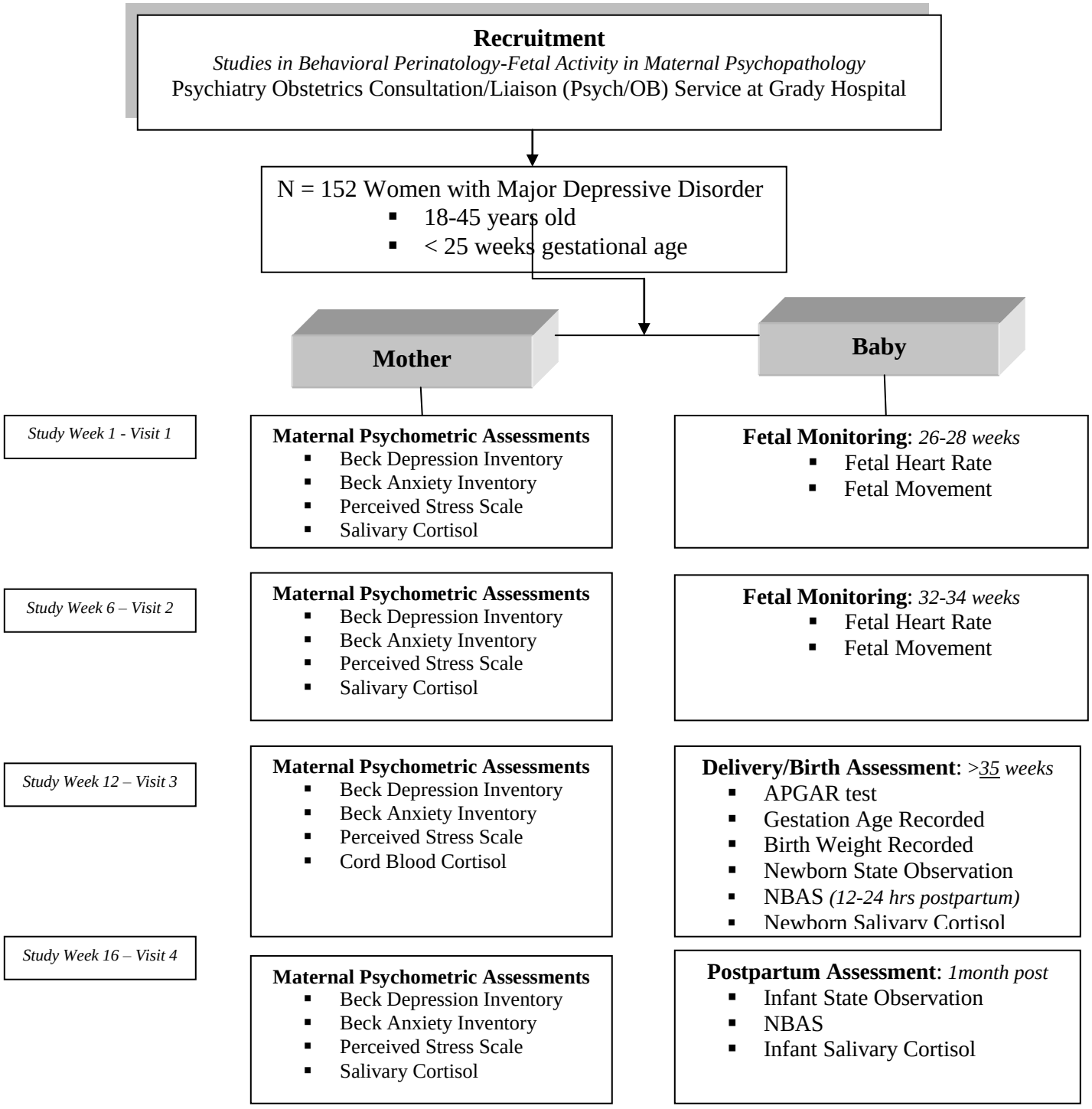


Figure 1. Time course and events of study participation.

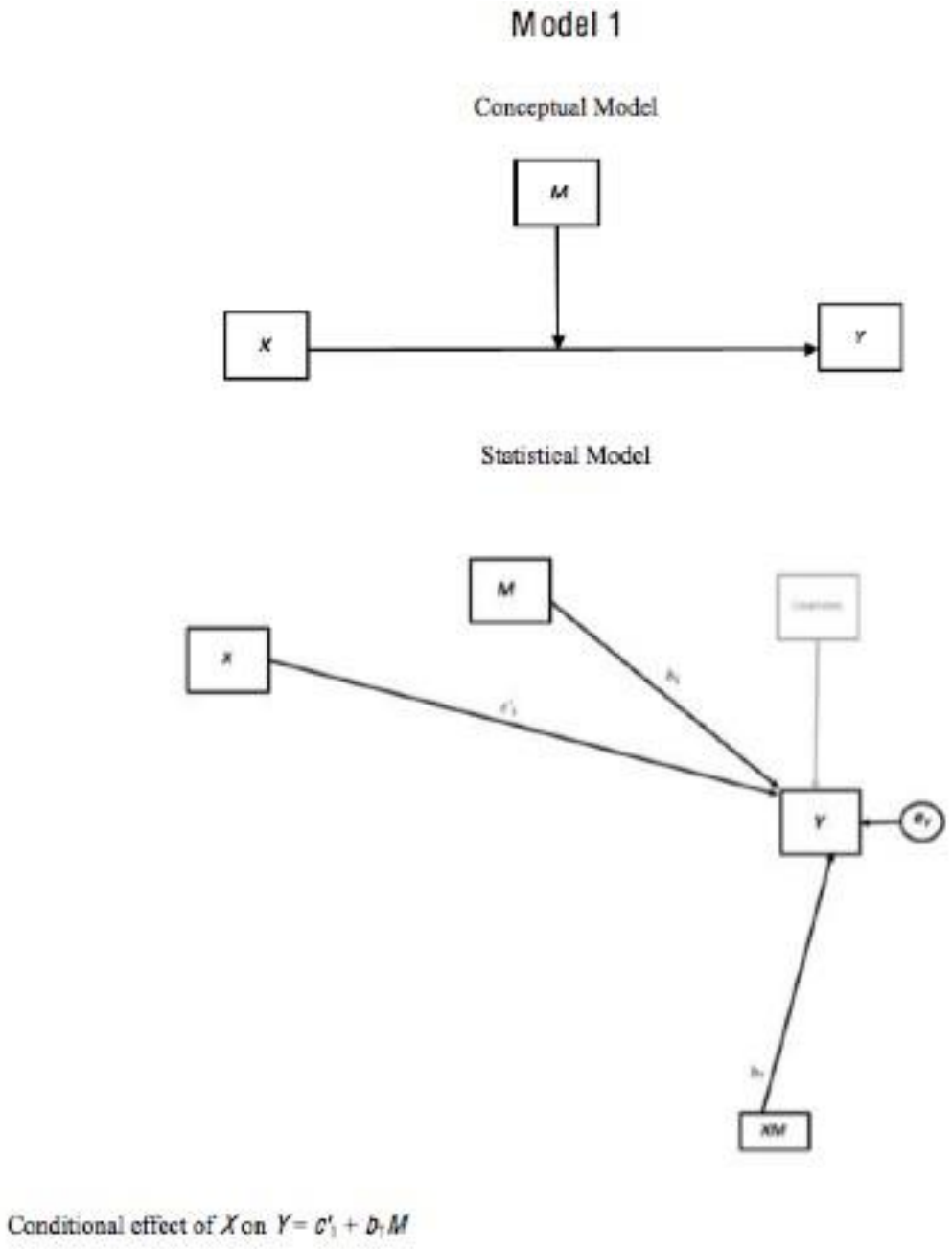


Figure 2. Preacher and Hayes PROCESS Model 1 of Conceptual and Statistical models for moderation analyses.

Appendix A

DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder

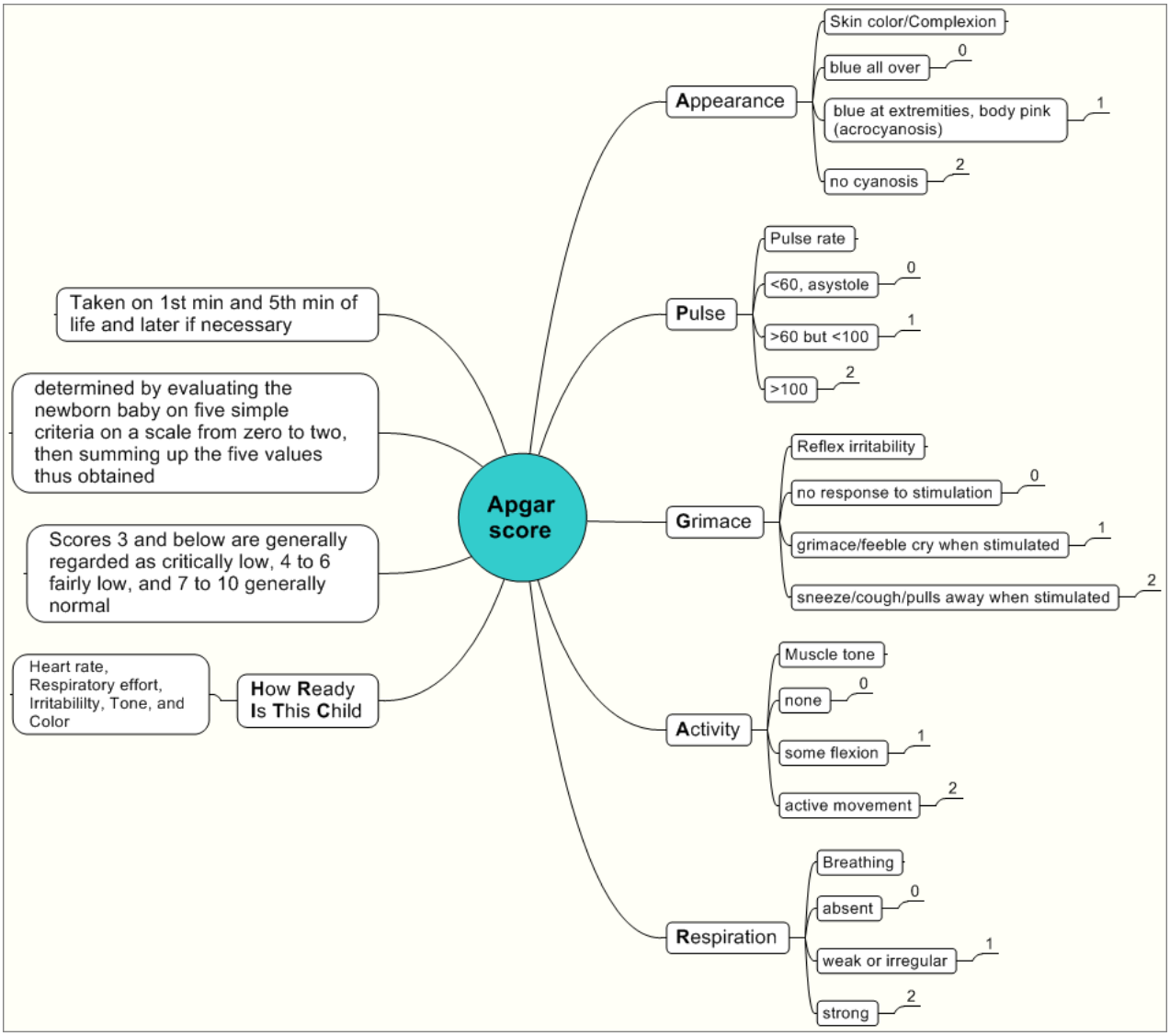
A. At least one of the following three abnormal moods which significantly interfered with the person's life:
    1. Abnormal depressed mood most of the day, nearly every day, for at least 2 weeks.
    2. Abnormal loss of all interest and pleasure most of the day, nearly every day, for at least 2 weeks.
    3. If 18 or younger, abnormal irritable mood most of the day, nearly every day, for at least 2 weeks.
B. At least five of the following symptoms have been present during the same 2 week depressed period.
    1. Abnormal depressed mood (or irritable mood if a child or adolescent) [as defined in criterion A].
    2. Abnormal loss of all interest and pleasure [as defined in criterion A2].
    3. Appetite or weight disturbance, either:
        - Abnormal weight loss (when not dieting) or decrease in appetite.
        - Abnormal weight gain or increase in appetite.
    4. Sleep disturbance, either abnormal insomnia or abnormal hypersomnia.
    5. Activity disturbance, either abnormal agitation or abnormal slowing (observable by others).
    6. Abnormal fatigue or loss of energy.
    7. Abnormal self-reproach or inappropriate guilt.
    8. Abnormal poor concentration or indecisiveness.
    9. Abnormal morbid thoughts of death (not just fear of dying) or suicide.
C. The symptoms are not due to a mood-incongruent psychosis.
D. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode
E. The symptoms are not due to physical illness, alcohol, medication, or street drugs.
F. The symptoms are not due to normal bereavement.

DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The person finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months).
   Note: Only one item is required in children.
   1. restlessness or feeling keyed up or on edge
   2. being easily fatigued
   3. difficulty concentrating or mind going blank
   4. irritability
   5. muscle tension
   6. sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

Appendix B

The APGAR Score



Appendix C

Sample of Neonatal Behavioral Assessment Scale Scoring Form

NBAS SCORING FORM

Name Sex Date of birth
Gestational age Weight Height Head circumference
Mode of delivery Length of labor Apgar scores
Parity Type of feeding Examiner Date of examination

	Infant behavior 9 8 7 6 5 4 3 2 1	Comments
HABITUATION		
Response Dec.—Light		
Response Dec.—Rattle		
Response Dec.—Bell		
Response Dec.—Foot		
SOCIAL—INTERACTIVE		
Animate Visual		
Animate Vis. + Aud.		
Inanimate Visual		
Inanimate Vis. + Aud.		
Animate Auditory		
Inanimate Auditory		
Alertness		
MOTOR SYSTEM		
General Tone		
Motor Maturity		
Pull-to-Sit		
Defensive		
Activity Level		
STATE ORGANIZATION		
Peak of Excitement		
Rapidity of Build-up		
Irritability		
Lability of States		
STATE REGULATION		
Cuddliness		
Consolability		
Self-Quieting		
Hand-to-Mouth		
AUTONOMIC SYSTEM		
Tremulousness		
Startles		
Lability of Skin Color		
Smiles	☐	

Appendix D

Beck Depression Inventory

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____ Page 14 patient inits: _____

Baseline

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

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_____ Subtotal Page 1

Continued on Back

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NR15645

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 15 patient inits: _____

Baseline

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2
_____ Subtotal Page 1
_____ Total Score

NR15645

Appendix E

Beck Anxiety Inventory

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the **past month,** including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring - Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____.

Appendix F

Perceived Stress Scale

Perceived Stress Scale

Name _____Date _____

Age _____ Gender (*Circle*): **M F** Other

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**