Temporal Associations between Prenatal Psychosocial Context and Birth Outcomes

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Abstract

Background: In the United States approximately one in eight babies is born preterm (before 37 completed weeks gestation), and one in twelve infants are born low birthweight (<2500 grams). These poor birth outcomes lead to neonatal morbidity and mortality as well as lifelong developmental and health issues that affect both the quality of life for families and convey a costly economic burden to these families and the public. Psychoneuroimmune interactions in response to stressful events or conditions alter cell signaling throughout the body During pregnancy, the maturing placenta is an active endocrine and immune organ; however, its' contributions to stress processing evolve as the pregnancy progresses. Approximately thirty percent of preterm births are attributable to endocrine immune changes that are related to stress processing.

Purpose: To evaluate the evolutionary framework of Adaptive Reproduction a theoretical basis for understanding how environmental stressors and psychoneurological states impact birth outcomes. Two hypotheses were tested: 1) does the impact of stress, depression, tobacco use and social support on adverse birth outcomes vary across the gestation? And 2) does the experience of perinatal intimate partner violence (IPV) affect the timing of the impact of stress, depression, tobacco use and social support on birth outcomes?

Sample and Setting: The sample included women involved in the BabyBEEP study (R01 NR05313) that evaluated the efficacy of a smoking cessation intervention for low-income pregnant women (N=695). Data was collected between 2002 and 2006 in 21 counties in rural Missouri. Thirty-four percent of the sample experienced perinatal intimate partner violence.

Methods: Data was restructured for secondary analysis using a multilevel structural equation model.

Findings: Both hypotheses were supported by the analysis. When controlling for the other variables, stress and social support have paradoxical effects at different stages of pregnancy. In women experiencing perinatal IPV, depression, particularly prior to 24 weeks, is associated with both low birthweight and preterm birth.

Conclusion: Adaptive reproduction provides a plausible explanation for why psychoneuroimmune alterations sometimes lead to preterm birth and low birthweight . This provides a theoretical basis for how community and individual level preconceptional and prenatal interventions aimed at enhancing functional social support and stress resilience improve outcomes.

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Introduction

This study is undertaken to elucidate vulnerable periods during pregnancy that may be amenable to intervention in order to improve outcomes. Specifically, this is an examination of the temporal relationships between environmental stressors and social support and the maternal psychoneuroimmune activity that leads to adverse birth outcomes. It will examine the relationships between intimate partner violence, perceived stress, tobacco use, social support, anxiety and depression at various gestational ages and their impact on gestational length and birthweight.

The Impetus for Prenatal Stress Process Research: Prenatal Care, Policy and Ethics

The goal of prenatal care in public health policy and interventions is to maximize healthy birth outcomes and minimize maternal and fetal harm across the entire population. Reducing disparities in birth outcomes related to stress exposures surrounding pregnancy directly addresses this duty. As problems are solved and new questions are explored, the focus and breadth of public duties, debates and prenatal care delivery have evolved. When the care of women during pregnancy and birth was wrest from midwives during the early twentieth century by physicians who championed the cause of a single medical standard for obstetrical care, their stated objective was to decrease maternal morbidity and mortality (Alexander & Kotelchuck, 2001; Wilson, 1996). Federal funding by the Sheppard-Towner Act from 1922-1929 demonstrated that there was public support, albeit fluctuating, for reducing maternal and infant mortality through the provision of public health services (Moehling & Thomasson, 2012).

American nurse-midwives' identified infant outcomes as an objective for prenatal care in that era in order to improve overall child health (Breckenridge, 1933, 1981). Nurse-midwives have codified this imperative to work towards reducing the incidence of low birth weight, premature birth, and infant mortality as an essential part of their role (American College of Nurse-Midwives Division of Standards and Practice, 2013). But the idea that prenatal care might affect infant outcomes did not enter the published medical discourse until the mid-twentieth century (Anderson, 1955; Eastman, 1947).

As public consideration that prenatal care might influence birth outcomes grew, funding for the provision of this care was eventually arranged. During the 1960s, there was a shift in the way that maternal care for low-income women was financed, which affected the provision of care. At the onset of the decade, middle class women who had access to private obstetrical care were encouraged to have a complete physical exam before pregnancy, and then attend prenatal visits approximately 12-14 times before the birth. Care delivered in this manner had been the standard since the 1930s (The Children's Bureau, 1930, 1962), and remains the framework for traditional antenatal care today. In the early 1960s, low-income women in the United States of America often did not have the resources to obtain private obstetrical care. For these women, prenatal care, if available at all, was largely delivered in hospital based clinics or, in rare instances such as the Maternity Center Association of New York City and the Frontier Nursing Service by nurse-midwives who held local clinics and made home visits (Keeling, 2007). Then, in 1961, President Kennedy convened a "Panel on Mental Retardation," which concluded in their 1962 report, that federal action was needed to address and try to prevent intellectual

disabilities (Bazelon & Boggs, 1963). Federal legislators were informed that poor women were having premature births and complications at the rate of two or three times the national rate, leading to infants with sequelae such as brain damage (United States Children's Bureau, 1964). In response to these concerns, Title V of the Social Security Act was amended in 1963, authorizing federal matching funds to states or localities for the provision of maternity and infant (MIC) care:

> The major objective of the maternity and infant care projects is to find the more vulnerable patients early in pregnancy and to provide care for them. These are patients who the State or local health agency determines will not receive necessary health care because they are from low income families or for other reasons beyond their control (United States Children's Bureau, 1964, p.2).

Today the moral imperative to preserve and protect potential life through prenatal care is so firmly entrenched in the public psyche that in 2004, the Centers for Disease Control changed their official definition of prenatal care to include preconceptional health services in hopes of affecting infant outcomes (Johnson, Posner, Biermann, & Cordero, 2006). However, there are still not any federal policies mandating funding for screening, vaccination or counseling during the preconceptional period (MACPAC, 2013). Recently there have been two federal initiatives specifically targeting the goals of maximizing healthy birth outcomes and minimizing maternal and fetal harm through the provision of care during pregnancy. The advent of the Patient Protection and Affordable Care Act of 2010 (ACA) has brought increased funding to Title V of the Social Security

Act, securing the first of these programs. The second project is funded through the Centers for Medicare & Medicaid Services (CMS).

The ACA(2010) authorized the establishment of the Maternal, Infant and Early Childhood Home Visiting Program (MIECHV), as an Amendment to Title V of the Social Security Act, and appropriated 1.5 billion dollars toward its implementation, in recognition of the evidence that home visiting programs lead to improved health and development outcomes for women and children. MIECHV is intended to implement evidence based home visiting programs. The legislation mandates that States demonstrate improvement in seven benchmark areas, including improving antenatal and postpartum health for mothers and babies and reducing domestic violence, as a condition for receiving continued funding of these programs.

Then in 2012, CMS announced its Strong Start for Mothers and Newborns Initiative (Centers for Medicare and Medicaid Services, 2012), in an effort to reduce preterm births (PTB) and improve outcomes for newborns and pregnant women. This encompasses two programs; the first is a public-private partnership and awareness campaign to reduce the rate of early elective deliveries prior to 39 weeks for all populations. The second component provides grant funding to test the effectiveness of enhanced types of prenatal care that may reduce the incidence of PTB among pregnant Medicaid or Children's Health Insurance Program (CHIP) beneficiaries at high risk for preterm births.

Yet serious contradictions on this topic exist in the public discourse, as illustrated by the ongoing congressional debates surrounding full enactment or repeal of the Health

Care and Education Reconciliation Act of 2010 (ACA), and the lack of funding mandates for preconceptional care. The ACA is perhaps the most significant piece of legislation to affect the healthcare of women since federal funding of maternity care for low-income women was legislated through the amendment of Title V in 1963 (United States Children's Bureau, 1964). The ACA mandates insurance coverage, including coverage for prenatal care, and provides options for low and middle wage earners to gain access to health insurance through insurance exchanges and provides premium subsidies to alleviate some of the economic constraints that previously impeded access to care for those who fell between indigent and wealthy (MACPAC, 2013).

Nonetheless, the United States Congress, as of the end of September 2013, had made 46 attempts to defund the ACA (Kapur, 2013), revealing significant cultural ambiguity about whether or not to recognize any type of health care as a public duty, much less prenatal care in particular. Arguments for respect of personal autonomy obscure other *prima facie* duties regarding when the state has an obligation to provide care. This is a cultural struggle between a deontological right's based approach and distributive or utilitarian approaches. Prenatal care in the United States has been routed in both social justice and utilitarian approaches. In addition to the justice focus on ameliorating burdens that necessarily befall some members of society and not others, programs of research and routines for nursing care evolved in an effort to decrease the social and economic costs of various types of reproductive failure or poor reproductive outcomes. Prenatal care services may not have any intrinsic value; this care is not simply

a consumer product or good, but also a supportive presence that contributes to one's ability to lead a good life.

It is a reasonable goal of prenatal care to not only work to preserve the life of mother and baby but also to build capacity for resilience in both. Current thinking suggests that numerous prenatal events affect the trajectory of a pregnancy and lifelong well-being (e.g. Barker, 2004; Christian, 2012; Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012). Maternal hypothalamic-pituitary-adrenal (HPA) axis activation in response to stress has been implicated in adverse reproductive outcomes for quite some time (Lockwood & Kuczynski, 1998). It is a suggested mechanism to explain ethnic disparities in reproductive outcomes such as preterm birth and low birthweight babies (Alexander & Cornely, 1987). The emerging field examining the psychoneuroimmunology (PNI) of pregnancy is specifically concerned with understanding the deleterious effects and mechanisms of environmental and chronic psychosocial stress on pregnancy and the developing fetus (Coussons-Read, Okun, & Simms, 2003). Reproductive PNI investigates how the presence and appraisal of these stresses, through HPA interactions, affects the body's defense against infection, and may create aberrant embryonic and fetal development. Developing an understanding of these processes can provide nurse-midwives, nurses, and physicians with a clearer understanding of when and how adverse outcomes evolve. This will provide new opportunities for, and better timing of interventions to alleviate birth outcomes.

Justification of Study

In the United States approximately 1 in 8 babies is born before 37 completed weeks gestation, which is considered premature or preterm, and 1 in 12 infants is considered low birthweight (LBW), weighing less than 2500 grams (Hamilton, Martin, & Ventura, 2011). This leads to neonatal morbidity and mortality as well as lifelong developmental and health issues that affect the quality of life for entire families (Allen, Cristofalo, & Kim, 2011; Beck et al., 2010). As advances in technology have led to decreased mortality rates, there has been a concomitant rise in short and long-term morbidity associated with prematurity (Allen et al., 2011).

Aside from the quality of life issues for affected families, the cost of these difficult reproductive outcomes is huge. According to an Institute of Medicine's report (Behrman & Stith Butler, 2006), prematurity creates an economic burden to society of at least $26.2 billion dollars annually. These economic expenditures are staggering, but the toll on quality of life for affected individuals, their families and communities is incalculable (Beck et al., 2010).

There is an urgent need to explicate the mechanisms that lead to these outcomes. Once we understand the mechanisms at work, we can begin to develop and implement effective interventions to decrease the incidence of these adverse outcomes. Data suggests that at least 30% of preterm births cannot be explained by medical pathology such as infection or disease state but is rather a result of a maternal stress event (Lockwood & Iams, 2004). This dissertation will attempt to address the gap in the

literature related to the timing of these stress events, and the relationship between timing of the events and birthweight and length of gestation.

Maternal depression has been associated with adverse birth outcomes (Grote et al., 2010). There are very specific stages in gestation when environmental exposures to some noxious agents are linked to neurodevelopmental disorders. Thalidomide exposure between day 20 and 24 of gestation is an example of this occurence (Strömland, Nordin, Miller, Akerström, & Gillberg, 1994). This suggests there may also be specific windows for harmful exposures to other biological or psychological events during gestation. Associations between maternal smoking behaviors and risk of abnormal neurodevelopment are well established (Wehby, Prater, McCarthy, Castilla, & Murray, 2011), but the timing of these exposures related to poor outcomes has not been examined.

Home visiting programs (Olds, 2002), group prenatal care (Ickovics et al., 2003, 2007), yoga (Narendran, 2005) and smoking cessation programs (Bullock et al., 2008; Gaffney, Baghi, & Sheehan, 2009) are examples of nursing interventions that attempt to mitigate the adverse effects of stress on pregnancies. Improving our understanding of the timing and physiology of these processes during pregnancy will provide opportunities to improve the efficiency and effectiveness of these interventions, and may well point towards other opportunities to intervene.

Telephone and group support interventions run by nurses and nurse-midwives are therapeutically contrived social supports that are associated with decreased stress and depression in the case of telephone support during pregnancy (L. F. Bullock, Wells, Duff, & Hornblow, 1995) and longer gestations with higher birthweights in the case of group

prenatal care (Ickovics et al., 2003, 2007). The literature is silent on whether there are times during pregnancy when these interventions are most predictive of improved outcomes.

Research Question and Hypotheses

For this dissertation, a secondary data analysis will be performed on data collected through an R01 NR05313, which was done to evaluate the efficacy of a smoking cessation intervention for pregnant women, in order to answer the following research question: Are different levels of stress, depression, and social support at any particular month of pregnancy more highly associated with gestational length or birthweight after controlling for tobacco use?

The hypotheses and specific aims are as follows:

Hypothesis #1

The impact of stress, depression, social support and tobacco use on adverse birth outcomes varies across gestational time periods.

Hypothesis #2

The pattern of impact of stress, depression, social support and tobacco use on adverse birth outcomes will vary in different patterns for women who experience IPV in the year before or during pregnancy compared to women who are not currently experiencing IPV.

Specific Aim #1

To identify the latent variables in the BabyBEEP dataset relating to stress, depression, anxiety and social support

Specific Aim # 2

To determine the linearity of the relationship among tobacco use and the latent constructs of stress, depression, and social support over time.

Specific Aim #3

Determine the differences in patterns of stress, depression, tobacco use and social support impact across time on gestational length and birthweight in pregnancies exposed to abuse compared to those not exposed to abuse:

a. Determine the association of tobacco use and the latent variables (social support, stress, and depression) at different gestational ages.

b. Determine the impact of the latent variables on gestational length and birthweight after controlling for tobacco use during pregnancy.

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Chapter 2: Literature Review

This review of the literature begins with a discussion of the theory of adaptive reproduction (AR), which is the proposed theoretical model for this research. Contrasting theoretical models for stress process research in pregnancy are discussed as well. The review continues with an overview of the evolution of stress process theory and discussion of psychoneuroimmunology (PNI) literature on the PNI of pregnancy, depression, stress and social support, the dependent variables of interest in this study. Literature on specific stressors that exist in the study population, intimate partner violence and tobacco use, is then reviewed. Subsequently the outcome variables of interest, premature birth and LBW are discussed. This is followed by a discussion of current understanding of maternal placental interfaces, the basis for study hypotheses. Finally, literature review concludes with a discussion of the limitations and advantages of secondary data analysis.

Theoretical Models for the Study of Stress Processes and Birth Outcomes

Adaptive Reproduction

The theoretical perspective of adaptive reproduction proposes that adverse birth outcomes may not occur as a result of a broken physiologic mechanism, but instead could be adaptive (Wasser & Isenberg, 1986). Wasser and Isenberg propose that biological adaptive mechanisms that limit reproduction in other mammals, especially those that have hormonal origins, can be useful in understanding human reproductive outcomes. This framework suggests that as resources become scarce, many species, including

humans, limit their reproductive activities, until there is a greater likelihood that the mother and her community could insure that the new offspring would survive.

From the perspective of evolutionary biology, our physiology strives to maximize lifetime success at reproducing offspring who can survive and thrive to reproduce themselves. As a consequence, premature birth, poor fetal growth, and perhaps even neurodevelopmental compromises represent vestigial efforts to enhance the woman's chances of successfully reproducing, though at the expense of a particular fetus. Rather than being a mechanical failure, preterm birth (PTB) has been viewed by reproductive biologists as an adaptive strategy in response to environmental conditions (Wasser & Barash, 1983a).

Interruption of a current pregnancy can be a physiological consequence of an environmental assessment by the maternal system that conditions are not optimal for supporting new offspring (Wasser & Barash, 1983a). This is an adaptive failure of a specific instance of reproduction in order to maximize the chance of overall lifetime reproductive success (the chance that offspring will survive to reproduce their own offspring). The theory of adaptive reproduction (AR) has not yet been fully iterated in human beings. Although biologists have long utilized this concept to discuss the genetic drive to maximize the chances of successfully reproducing (e.g. Kaplan, 2004; Klussendorf, 1946; Zhang, 2004), and physicians have used the concept in literature discussing infertility (e.g. Barnea & Tal, 1991; Bergstrom, 1992; Rote & Stetzer, 2003; Wasser, Sewall, & Soules, 1993), it has rarely been utilized in nursing. The exception is Floyd's (1981) discussion of nursing care considerations for couples who have conceived

after a pregnancy loss. Aside from an opinion piece by Wasser (1999) this framework has not been utilized to explain adverse birth outcomes involving live births. However, as Wasser suggested, principles of adaptive reproduction can neatly explain the otherwise perplexing neuroendocrine and neuroimmune responses to adversity that are seen in many human pregnancies. This explanation will ultimately be described on the level of cell signaling between the mother, placenta and fetus.

The theory of AR combines the concepts of adaptation and reproductive failure. Reproductive failure occurs when a concerted attempt to conceive, bear and raise offspring does not produce a healthy, functional member of the next generation (Wasser, 1999). This is an adaptive mechanism, in two senses. First, it refers to the ability of the woman to respond to environmental context by continually adapting her physiologic response to changing socio-environmental circumstances. And secondly, it refers to the epigenetic pruning that has occurred over generations to favor phenotypes that provide a person or group of people with reproductive advantage over others. This polysemic definition of adaptation adds flexibility to the AR model. It allows for the modeling of historical, cultural, social and appraisal issues as well as molecular level signaling circuits that are involved in reproduction and modulate over time (see Figure 1). In this model, *broad psychosocial context* refers to the overall health and adaptability of the entire community. This encompasses the physical and social setting in which people live, including culture, and socioeconomic environment. Issues such as safety and access to resources such as food, water, adequate housing, opportunities for education, meaningful work or work that provides a living wage and intact social structures are all included

within the broad psychosocial context. An individual's mental health is reflected in the *psychoneurological context* in the AR model. The *nuclear social-behavioral context* refers to an individual's immediately available social resources, surroundings and current behaviors. *Cell signaling markers* in the AR conceptual model denote the substances and processes that transmit information about the environment to individual human cells. The final component of the AR framework is *reproductive outcomes*, usually utilizes measures of preterm birth, birthweight and fetal growth restriction which are the major determinants of health during the first 12 months of extrauterine life.

AR proposes that human reproduction is a robust biological event that follows a specific logic to achieve success. The complex immunomodulatory systems of the placenta commandeer reproductive processes in response to socio-environmental stressors. They can end a pregnancy early or deprive a fetus of the full complement of maternal resources to promote the woman's chances of overall lifetime reproductive success. This model assumes that modern human females are genetically predisposed to maximize the parenting effort they invest in each offspring (Troisi, 2001) and their physiology is inclined towards giving birth in resource rich social environments. Aborting a pregnancy before full-term is an adaptive behavior if the scarcity of social resources is likely to be temporary (Wasser & Barash, 1983b). There are two specific mechanisms that Wasser proposes to describe environmental influences on reproductive difficulties in humans: reproductive suppression (Wasser & Barash, 1983) and reproductive filtering (Wasser, 1994).

Reproductive suppression

A strict interpretation of reproductive suppression refers to both the ability of females to inhibit the reproductive capabilities of those around them, in order to maximize the resources available for the suppressor's offspring, and to the responsiveness of females to these suppressing influences. In non-human primate groups, decreased reproductive performance in subordinate females is well documented (Kaplan & Manuck, 2004). The mechanisms within the placenta that work to optimize reproduction in this way have not altered as humans have become more adept at maintaining extra-uterine life in the NICU environment.

Reproductive filtering

The reproductive filtering model (RFM) is more broadly applied. Many biologists postulate that there are several kinds of environmental signals that cue physiological mechanisms to limit reproduction when conditions are not optimal (Wasser & Barash, 1983a). RFM suggests that infertility, early pregnancy loss, and PTB can be adaptive responses to environmental stressors, and most specifically to psychosocial stressors. When current conditions are less than ideal for raising a baby, adaptive mechanisms are triggered that lead to prevention or disruption of a pregnancy.

Pointing to a large body of literature examining reproductive success and failure in non-human animals, Wasser (Wasser & Barash, 1983; Wasser, 1999) reports that social stressors are the main limiting factor for reproductive success in animals who are highly socially organized, breed year round, and have dominant couples as head of social groups. Adverse reproductive outcomes occur most commonly in these species when

there is lack of social support, significant competition for resources, or some sort of social disarray.

Why use Adaptive Reproduction?

Poor reproductive outcomes have largely been resistant to obstetrical and nursing interventions in the last century. For instance, in spite of tocolytic therapies designed to prolong pregnancies experiencing premature labor, preterm birth rates have actually increased (Martin, 2010). Grasping the nature of the phenomena that produces these outcomes is crucial to the development of effective and/or efficient interventions. The AR framework is beneficial for this research because of the unique lens through which it frames research questions about the underlying mechanisms. This is a theory of ultimate causation; it explains *why* something happens. It is important to distinguish between ultimate theories and theories of proximal causation, which explain a mechanism, or *how* something happens (Mayr, 1982). AR suggests that more so than other types of stressors, lack of socio-environmental resources is likely to lead to poor reproductive outcomes. When testing proximal mechanisms, the research questions need to be tied to an ultimate epistemological standpoint, such as AR.

Alternative Models

Biomedicine

Biomedical theory is primarily focused on pathophysiology of the individual (Hahn & Kleinman, 1983). This common theory of disease views adverse birth outcomes such as preterm birth, low birthweight (LBW) and neurodevelopmental delays as results of a malfunctioning system, rather than as a protective biobehavioral mechanism

designed to promote success on some level (such as maternal reproductive success or the survival of the species). Biomedicine has not produced adequate interventional strategies, and can only identify pathogenic causes for a fraction of the poor outcomes. From a biomedical perspective, Lockwood and Kuczynski (1999) described the Hypthothalamic-Pituitary-Adrenal (HPA) axis activation seen in pregnancies experiencing poor outcomes as "pathogenic" (p.5), suggesting that somehow the woman's HPA system is broken. Biomedicine does not address environmental issues or credit human physiology for responding appropriately to changing environmental stimuli, which makes it a poor choice for research on the environmental/biobehavioral causes of poor reproductive outcomes. A recent call for biomedical education to include evolutionary biology (Nesse et al., 2010); suggests this theory is now being called into question by some members of the profession that almost singlehandedly advance it.

Stress models

The allostasis model described by McEwen and Wingfield, (2003), along with its predecessor theories, Cannon and Bernard's homeostasis (Cooper, 2008) and Selye's (1955) general adaptation theory, are also mechanistic proximal theories, and as such should not be directly compared to AR. One weakness of these theories is that they consider a specific stress response to be nonspecifically induced (Selye, 1955). Also, the focus on cumulative load in the allostasis model does not accommodate the idea of fluctuating levels of risk and physiologic response suggested by recent research (Southcombe, Tannetta, Redman, & Sargent, 2011). Finally, they do not account for

psychoneuroimmunological differences due to varying individual stress responsivity (e.g. the variation in degree of adrenaline or cortisol response).

Other evolutionary development models

AR is one of a group of evolutionary developmental models that propose alternatives to biomedical pathogenesis and the allostasis model of stress processing. These evolutionary models all attempt to explain this individual biobehavioral variation in response to stress .

Adaptive calibration

To address these differences in stress reactivity, alternative theories have arisen. Adaptive calibration (Del Giudice, Ellis, & Shirtcliff, 2011) is an epigenetic theory that suggests a person's phenotype changes in response to stressors, in order to regulate how much neural processing or cell-signaling input the system actually receives in the presence of a threat. It shares many commonalities with AR, but its focus on physiologic responsivity is too narrow to fully explore the multifaceted stress process in pregnancy. It focuses on individual phenotypical differences that regulate neural or cell-signaling input a person processes in the presence of a threat. Variations in responsivity to prenatal stressors may explain disparities in fetal growth and development (Bergman, Sarkar, Glover, & O'Connor, 2010; Sarkar, Bergman, Fisk, & Glover, 2006). But the only measures of stress responsivity that appear in the literature are laboratory induced, making it impractical for large-scale study. Furthermore, their dependent variable is threat appraisal; it falls short of explaining the entire path towards birth outcomes.

Social baseline theory

Social baseline theory (SBT) (Beckes & Coan, 2012; Coan, 2008, 2010) suggests that modern human beings are hard-wired to be in relation and close proximity to other humans, and that the presence of others modulates the physiologic PNI response to stressors (Beckes & Coan, 2012). According to Coan (2008), "individuals in attachment relationships literally become part of each other's emotion regulation strategy." (p. 262).

External threats present less risk to members of a group, and resources are easier to procure, thus accounting for the variation in stress reactivity and adverse outcomes. Thus pregnant women who have strong, functional social bonds will have less stress reactivity in response to a threat, compared to women who do not, and therefore will have fewer adverse outcomes. To date, physiologic research involving SBT has been exclusively with neural imaging, and has not been conducted with pregnant women or young children. This fascinating theory also falls short because it does not account for the neuroimmune communication that alters birth outcomes.

AR is an ultimate model that accommodates all of the variables in existing literature (environmental, social, psychological, appraisal/responsivity, neuroendocrine and neuroimmune) that contribute to adverse birth outcomes. As new biobehavioral techniques and data emerge aspects of the framework will need to be refined. Starting with a broad evolutionary framework allows for these proximal developments from the environmental through the molecular level.

Psychoneuroimmunology

Several physiological systems are in continual communication with each other to respond to the external world. The sensory systems and thoughts of the brain create cellular responses through the endocrine, neurological and immune system function within the body (Ray, 2004) The field of study that examines these related processes is Psychoneuroimmunology.

Stress Process Theory

Stress can be described as a physiologic response to environmental threats or demands (Cohen, Kessler, & Underwood, 1995). Environmental demands or threats are considered stressors. Selye (1936, 1955) described the first stress theory, often referred to as general adaptation syndrome (GAS), in which he described the non-specific (meaning that they occur in everyone) reactions to stressors. Accordingly, both the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis exist in part to respond to stress. Organisms react in three phases: alarm, resistance, and then exhaustion/recovery (Selye, 1955). Specific stresses could be aversive or not, and if the organism survives the threat, according to the GAS model that assumed the principles of homeostasis (Cooper, 2008), the body returns to its original state or set point.

The Development of Psychoneuroimmunology

Interestingly, Selye's theory contained an immune link. Selye (1955) called an inflammatory response a "local adaptation syndrome" that at its most severe could lead to GAS. In 1975, Ader and Cohen proposed the idea that immune physiology could be conditioned to respond to environmental stressors. This led to the understanding that

physiological stress responses can be created through a person's thoughts and ruminations, one of the foundational concepts for the field of psychoneuroimmunology (PNI).

Psychoneuroimmunology (PNI) is a useful proximal theory that is consistent with AR. It examines the relationship between the mind's appraisal of the environment and physiologic health and well-being. This theory suggests that as environmental stressors are appraised by an individual, a physiologic stress response is triggered, which regulates the signaling of hormones, neurotransmitters and cytokines from the brain throughout the body (Besedovsky & Rey, 2007). PNI research examines the relationships between stressors, stress appraisal and the biological mechanisms that alter immune functioning.

A connection between the SNS and the immune system was confirmed by the research of Felten and Felten (1994) who demonstrated there are limbic-insensitive sympathetic nerve fibers extending from the brain to innervate bone marrow thymus and lymph tissue. The neural pathways that are first activated in response to stress along the catecholamine pathways often referred to as either limbic-insensitive, or limbic-sensitive circuits. Immediate threats are processed through the former system, which innervates the locus coerulus (Glaser, Rabin, Chesney, Cohen, & Natelson, 1999) and the paraventricular nucleus of the hypothalamus whose neurons extend into the posterior pituitary and bone and lymph tissue, while the latter system, originating in the amygdala, which is thought to be the source of signaling in response to apprehension of psychological stress (Herman & Cullinan, 1997). The signaling from these two systems initiates the subsequent endocrine and immune responses. Many substances can be

secreted from these fibers which can attach to lymphocytes to influence their behavior (Ader, Cohen, & Felten, 1995).

Besedovsky and Rey (2007) then explained the influence that the HPA-immune regulatory circuits, which control inflammation and auto-immune processes, had on neural processes through cytokines that cross the blood-brain barrier. The discovery that the brain, endocrine and immune system were in constant communication with each other, formed the basis of the PNI field. A classic review by Weigent, Carr, and Blalock (1990) demonstrated how the immune system not only receives sensory input from the neural systems, but also, through continual endocrine and immune signaling. This informs the brain of physiologic processing of distant cells and organs. This bi-directional functioning of the psychoneuroimmune systems is still not fully appreciated; researchers are only starting to acknowledge and examine the ways in which cell signaling can inform the brain's responses, thoughts and initiation of behaviors.

A meta-analysis of stress and immune related literature outside of pregnancy by Segerstrom and Miller (2004) demonstrated that brief stressors lead to immune modulation that promotes survival, health and well-being, while chronic stressors have unfavorable effects on health. Rassnick, Sved, and Rabin (1994) demonstrated that levels of cytokines, T lymphocytes, Natural Killer (NK) lymphocytes and B lymphocytes are reduced in circulation by psychological stress. Depression (Leonard & Maes, 2012) and anxiety (Salim, Chugh, & Asghar, 2012) are examples of chronic stress states that lead to alterations in immune functioning that can intensify vulnerability towards infectious diseases, allergies, autoimmune disorders and cancers.

The Psychoneuroimmunology of Pregnancy

Pregnancy is recognized as a state of elevated immune function. Numerous studies have demonstrated that innate immune processes are critical to all stages of pregnancy maintenance and success(Christiaens et al., 2008; Jabbour, Sales, Catalano, & Norman, 2009; Sacks, Studena, Sargent, & Redman, 1998; Sargent, Borzychowski, & Redman, 2006; Young et al., 2002). Innate immune cells prepare for and respond to the process of reproduction in much the same way that it responds to acute or naturalistic stressors. Endocrine and immune alliances evolve as hormones prepare the body for pregnancy, and then as the placenta matures, it develops the ability to centrally regulate endocrine and immune processes. The responses of these systems in pregnancy appear to be multilayered and complex events in which various coalitions form and dissolve throughout pregnancy, culminating in parturition. The central role of the placenta is the key to understanding why the sterile inflammatory responses of the immune system do not target and attack the semi allogeneic tissue of the fetus for removal.

All pregnant women experience elevated pro-inflammatory cytokines (PICs) in pregnancy (Challis et al., 2009; Fialová et al., 2006). However, there are significant relationships between above normal elevations in PICs during pregnancy, and both pregnancy pathologies such as preeclampsia (Sacks et al., 1998) and increased psychosocial stressors (Coussons-Read, Okun, & Nettles, 2007).

There is a growing body of literature demonstrating that psychological stress is connected to adverse birth outcomes and that the relationship between these two constructs is neuroendocrine or neuroimmune. For the most part this literature has

focused on the neuroendocrine processes (e.g Buss et al., 2009; Glynn, Schetter, Chicz-DeMet, Hobel, & Sandman, 2007; Jones et al., 2006; Kramer et al., 2009; Latendresse & Ruiz, 2010; Mancuso, Schetter, Rini, Roesch, & Hobel, 2004) with conflicting results. Immune mediators have not been sufficiently studied. This gap is significant because of the growing understanding that pregnancy is largely regulated by immunomodulatory processes of the innate immune system (e.g. Hickey, Patel, Fahey, & Wira, 2011; Houser, 2012; Jabbour, Sales, Catalano, & Norman, 2009).

Work by Coussons-Read, Okun, and Nettles (2007) in a sample of 52 pregnant women, were able to demonstrate that elevated stress and other psychosocial factors in pregnancy is associated with higher levels of C-Reactive Protein (CRP) and pro-inflammatory cytokines. They found that increased stress during the first and third trimester was associated with concurrent elevations in PICs and CRP. However, second trimester increases in stress or the presence of low social support were not associated with the same concurrent elevation in these inflammatory markers. Furthermore, recent research by Coussons-Read and colleagues (Coussons-Read et al., 2012) claiming that preterm birth is associated with elevated inflammatory markers across gestation, actually only evaluated women beyond the tenth week of pregnancy and at only two time points during gestation; this research leaves gaps that are still unanswered.

Recently, the placenta has been identified as one more critical member of this communication network during pregnancy (Fest et al., 2007; Mor, 2008). Thus, the PNI of pregnancy is defined as the study of neuroendocrine-immune-placental stress responses.

Dunkel Schetter and Glynn (2010) propose reducing stress models for pregnancy research to a three step path beginning with stressors, followed by mediators and ending in an adverse birth outcome. This modeling procedure will work well within a PNI framework. The framework described in Figure 1 illustrates how stressors within the broad or nuclear social context can be mediated by the psychoneurological context and cell-signaling processes which lead to birth outcomes.

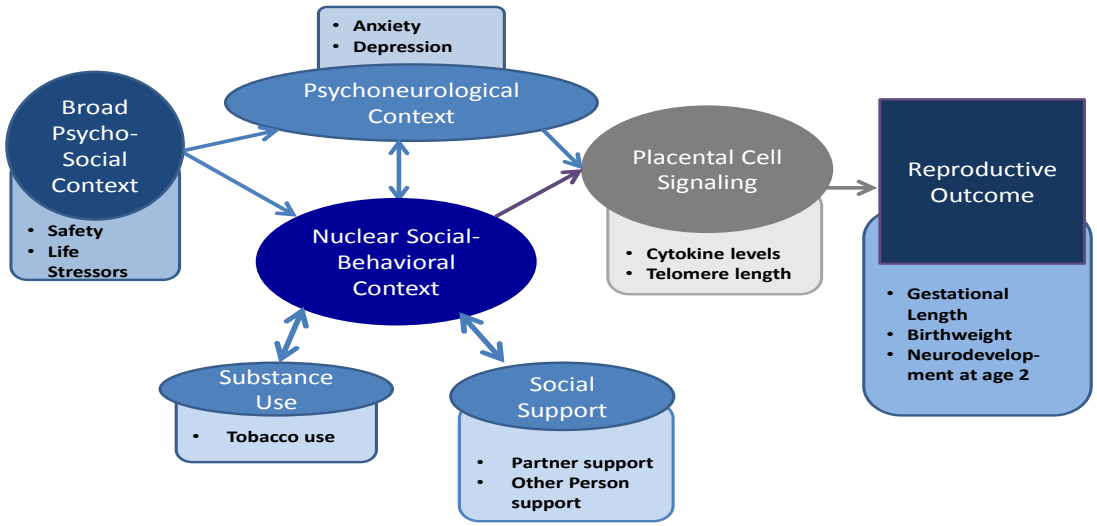

Figure 2.1: Conceptual model for Adaptive Reproduction. This model describes how both external (broad psychosocial and nuclear socialbehavioral) internal (psychoneurological) environmental influences are translated into cell signaling changes that lead to reproductive outcomes.

A recent model proposed by long-time stress in pregnancy researchers, Wadhwa, Entringer, Buss, and Lu (2011), focuses on a life-course perspective to explain the PNI complexities of the relationship between stress and preterm birth. While life-course theory holds merit as an explanation of epigenetic differences due to early programming,

they recognized the limitations for explaining variations in stress processing during pregnancy. Their group proposes that studying stress reactivity in pregnancy using ecological momentary assessment, which is repeated measurement on multiple variables, may help disentangle the issues related to the processing of stress in pregnancy. They believe this methodology; obtaining repeated measures throughout the pregnancy to minimize within subject variation will help explain stress reactivity changes as they impact preterm birth. But they fail to recognize that these measurements could be affected from two directions. These changes could be due to changes in environmental stimuli, but they are just as likely to be changed by the evolving PNI-placental milieu of pregnancy. Furthermore, this particular biobehavioral model only evaluates preterm birth, without considering other adverse outcomes.

McEwen and Wingfield (2003) theory of allostasis/allostatic load suggested that stability in the biological system is maintained through changing set points. Building on Selye's proposal, this theory suggests that although most short-term stressors effect an SNS and HPA axis response that is short-lived, if the system is constantly activated by appraisal of threats in the environment, an allostatic load develops, altering the ability of the HPA axis to initiate immune reactions, which ultimately contributes to morbidity. Relating this theory to pregnancy, Coussons-Read, Okun, and Simms (2003) suggest that this stress induced immunosuppression leads to adverse birth outcomes. The problem with this theory is that it does not account for differences that we see in the reactions of individuals to the same stressor or the same amount of perceived stress. Some women with these exposures experience adverse birth outcomes, and some do not. Perhaps these

differences exist for genetic and epigenetic reasons that are not easily captured in traditional psychological or sociological research.

Normal neuroendocrine activity during pregnancy

In normal pregnancy, there is an attenuation of both the HPA axis and the sympathetic nervous system responses to psychological and physiological stress (de Weerth & Buitelaar, 2005b; Engel, Berkowitz, Wolff, & Yehuda, 2005; Glynn, Schetter, Wadhwa, & Sandman, 2004; Glynn, Wadhwa, Dunkel Schetter, Chicz-Demet, & Sandman, 2001). According to Glynn and colleagues (2004), women do not express the same level of emotional response to stress in late pregnancy as they do earlier in pregnancy. Increasingly researchers are able to quantify how the stress responses as measured by psychological survey instruments reflect changes in metabolic processing issues. In a recent review, Dunkel Schetter and Glynn, (2010) describe the conflicting research about how these stress responses relate to actual birth outcomes.

During the second and third trimester, there is normal increased activity in the maternal-placental HPA axis. Maternal adrenocorticotropic hormone (ACTH) (Glynn et al., 2007) rises steadily, the maternal cortisol awakening response baseline is raised (Buss et al., 2009), and levels of circulating cortisol increase (de Weerth & Buitelaar, 2005a) leading to an escalation in production of the placental form of corticotropin-releasing hormone (CRH) (McLean & Smith, 2001).

Most circulating CRH in maternal serum is derived from the placenta. Maternal CRH is secreted into the portal system in the brain in such small quantities that it cannot be detected in systemic circulation (Latendresse & Ruiz, 2008). Placental CRH, which

rises mildly throughout the first 30 weeks of gestation, has the capacity to deactivate the inflammatory response at multiple levels to maintain immune tolerance of the pregnancy (Challis et al., 2009). There is a dramatic increase in the circulating levels of CRH at the beginning of the third trimester (Glynn et al., 2007; Sandman et al., 2006). Interestingly, this does not produce a corresponding elevation in maternal or fetal cortisol serum levels, which to some extent, can be explained by the enzymatic conversion of maternal cortisol into inactive cortisone by the placenta (Sun, Adamson, Yang, & Challis, 1999). The increased presence of CRH- binding proteins also renders much of this placental CRH inactive in the maternal circulation (McLean, 2001), thus limiting the production of maternal cortisol; this effectively dampens the response of the maternal HPA axis (de Weerth & Buitelaar, 2005b). Elevation in maternal serum cortisol levels in response to the high levels of CRH does not usually occur until the end of the third trimester when these binding proteins become less available, allowing cortisol levels to spike as labor approaches (Challis et al., 2009).

Response of the maternal-placental HPA axis in abnormal pregnancies

In women who experience PTB, the aforedescribed dampening effect has, from a biomedical perspective, been described as dysfunctional (Buss et al., 2009; Glynn et al., 2004; Mancuso et al., 2004). Cortisol, a hormone that is usually associated with anti-inflammatory activity, also inhibits release of prostaglandins during pregnancy. In animal models, however, as labor approaches, cortisol acts on amniotic membrane cells to increase production of prostaglandins (Challis et al., 2009). Buss et al. (2009) found that women who deliver prematurely not only have baseline cortisol levels higher than

women who deliver at term, but also have a more dramatic response to stress (stress reactivity). This alteration in cortisol responsiveness was predictive of PTB. Furthermore, women who experience particularly high levels of CRH early in pregnancy tend to deliver preterm, and those with very low concentrations of CRH are more likely to deliver post-term (McLean et al., 1995). Thus, it seems that hormonal behavior can predict the length of gestation.

Placental Physiology

The trophoblastic cells of the human placenta play a critical role throughout pregnancy, but especially during implantation, placentation, and parturition. The idea that the placenta is an immune barrier that protects the fetus from maternal rejection (Medawar, 1953) is outdated. The trophoblasts essentially commandeer the maternal immune system (e.g. Southcombe, Tannetta, Redman, & Sargent, 2011; Tilburgs, Claas, & Scherjon, 2010) and figure in the regulation of maternal endocrine function (Aye, Powell, & Jansson, 2012; Hogg, Price, Hanna, & Robinson, 2012). Our growing understanding of hypoxia, and its role in adverse birth outcomes such as preeclampsia and growth restricted infants, has provided a potential model for understanding the role of cell signaling cascades in acute events and disease processes that occur in offspring developmentally remote from pregnancy (Tissot van Patot, Ebensperger, Gassmann, & Llanos, 2012).

Psychoneuroimmunology of depression and anxiety

Mood, perception and immune functioning reciprocally influence one another (Maier, 2003). The growing understanding of how these variables interact is described in

this section, with particular attention being paid to the interaction of mood variables and immune functioning during pregnancy.

Psychoneuroimmunology of Depression

Prevalence estimates for depressive disorders in the United States stand at 9.5% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). An innate inflammatory response of the immune system appears in people suffering from depression (Pace et al., 2006; Zorrilla et al., 2001). C-reactive protein levels (Miller, Stetler, Carney, Freedland, & Banks, 2002) along with cytokine and NK cell changes have been documented (Irwin & Miller, 2007) in people with depressive symptomology, in both the presence and absence of other pathology.

Early PNI research on depression described stress and depressed states as suppressing immunity (Reiche, Nunes, & Morimoto, 2004). Initial studies found that there were fewer lymphocytes (Nunes et al., 2002) and fewer natural killer (NK) cells and T-cells (Zorrilla et al., 2001) in circulation in the presence of these conditions. But current understanding is that depression and anxiety appear to activate or reflect an activation of the immune system (Guloksuz et al., 2013; Maes et al., 2012; Salim et al., 2012). Fewer NK cells and lymphocytes in serum and plasma do not reflect less activation; these cells have been commissioned out of circulation and into the tissues where they are functioning. When the immune system is activated, symptoms of depression can appear that signal a reaction has occurred. In response to acute stress, the innate immune system signals the nucleus of cells to transcribe and produce pro-inflammatory cytokines (PICs). In turn, these PICs produce sickness behaviors such as

withdrawal, anhedonia, decreased sex drive, anorexia, and profound fatigue. Depression mimics these sickness behaviors (Maes et al., 2012), and reflects an activated innate immune system.

Depression in pregnancy

The literature regarding the impact of depression in pregnancy on neonatal outcome is mixed. For instance, there are studies that show no association between depressive disorders and preterm birth (e.g. Andersson, Sundström-Poromaa, Wulff, Aström, & Bixo, 2004; Kramer et al., 2009) and those that do show a significant correlation between these two variables (Dayan et al., 2006; Jesse, Seaver, & Wallace, 2003). Each of the above mentioned studies evaluated women in the second trimester with a single measurement of psychological surveys (Andersson et al., 2004; Dayan et al., 2006; Kramer et al., 2009) or a series of questions taken from other instruments (Jesse et al., 2003). The two studies that did not find a correlation each evaluated women in narrow windows of gestation. The Andersson group (2004) surveyed women between 16 and 18 weeks gestation, while Kramer and colleagues (2009) interviewed women between 24 and 26 weeks gestation. In contrast, the 2006 study by Dayan et al. evaluated women across an 8 week gestational period (from 20-28 weeks) and the earlier study by Jesse's group conducted their single interview between 16 and 28 weeks gestation. There are no longitudinal evaluations of depression and pregnancy outcome in the literature.

Psychoneuroimmunology of Anxiety

The prevalence of anxiety disorders in the United States is estimated to be 18.1% in the adult population (Kessler et al., 2005). Anxiety involves inappropriate or extreme

states of arousal exemplified by feeling afraid, uncertain or apprehensive (Hou & Baldwin, 2012). When these feelings interfere with normal daily functioning it is classified as an Anxiety Disorder, under the DSM-IV-TR (American Psychiatric Association, 2000). There is significant co-morbidity with depressive symptoms (Kessler et al., 2005; Unick, Snowden, & Hastings, 2009). During an episode of perceived fear or anxiety, the sympathetic nervous system (SNS) automatically activates even if the threat is not real. There appears to be a balance of pro-inflammatory versus anti-inflammatory cytokines that represent normal psychoneuroimmune function in healthy individuals (Hou & Baldwin, 2012). Leonard and Myint (2009) have described how chronic stress serves as an impetus for HPA axis and immune system changes that lead to anxiety and depression. Moreover, murine models have shown that increased PIC levels are commonly found in animals who are bred to exhibit an anxious phenotype (Fiore et al., 1998; Schrott & Crnic, 1996). Human subjects who scored as anxious on the Hospital Anxiety and Depression Scale (HADS) in one study had significantly higher levels of Interleukin-6 (Il-6) and lower levels of cortisol than their non-anxious counterparts, although there were not significant differences in these biomarkers between depressed and non-depressed subjects (O'Donovan et al., 2010). In a case-control study of women comparing those with anxiety and those who were non-anxious, the anxious women had decreased NK cell activity and altered cytokine behavior compared to control group (Arranz, Guayerbas, & De la Fuente, 2007). Chronic anxiety disorder has been shown to decrease cellular immune function and increase morbidity in patients with gastric disease (Zhou et al., 2005).

Again, longitudinal PNI studies and anxiety have not been done, which is a significant gap in the literature.

Anxiety in pregnancy

Anxious state has been correlated with gestational length in several studies (e.g. Andersson et al., 2004; Glynn, Schetter, Hobel, & Sandman, 2008; Lobel et al., 2008; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). Dunkel-Schetter's group has recently been arguing that 'pregnancy anxiety' is a specific phenomenon that is particularly associated with preterm birth (Dunkel-Schetter 2011; Dunkel Schetter & Tanner, 2012). Pregnancy anxiety consists of fears about the health and well-being of the baby, concerns about surviving the pregnancy, the birth, and the ability to parent. Given what is understood about the bi-directional nature of the psychoneuroimmune system, exaggerated anxiety (beyond proportions expected due to the normal concerns of pregnancy) may reflect signaling from the placenta to the brain that there is something abnormal taking place with the pregnancy, rather than the anxiety actually being the cause of the pregnancy. This is a nuance that has not yet been appreciated in the literature.

In a recent study by Conde and colleagues (Conde et al., 2010), increased anxiety as measured by Spielberger's(1983) State-Trait Anxiety Index (STAI) was associated with decreased fetal growth at 20-22 weeks gestation. This study actually measured anxiety in both the first and second trimesters; it was second trimester anxiety that correlated with lower fetal growth.

There are not many studies correlating prenatal anxiety with LBW or infant neurodevelopment. One study examined the associations between prenatal anxiety measured at two time periods during pregnancy (essentially before and after 20 weeks gestation) and behavior problems in their offspring at age 4 years (O'Connor, Heron, Golding, Beveridge, & Glover, 2002). In their sample of over 7000 mother-child dyads, after controlling for postnatal maternal mood disorders, they found strong significant correlations between prenatal anxiety and increased risk of behavior problems (hyperactivity, emotional regulation and conduct). In contrast, a more recent study has found that maternal prenatal affect alone did not correlate with 4 month-old infant responsiveness or cortisol levels, except when the interaction between antepartum mood and postpartum maternal sensitivity to the infant was included in the analysis (Kaplan, Evans, & Monk, 2008).

Social Support during Pregnancy

Social support is a modifiable variable in a woman's environment during pregnancy. Bullock, Wells, Duff, and Hornblow (1995) demonstrated how telephone support interventions by nurses improved levels of stress, anxiety and depression in a group of pregnant women. Group prenatal care that combines physical assessment, education and social support, appears to decreases PTB rates and lowers rates of LBW in populations with extreme health disparities (Ickovics et al., 2003; Ickovics, et al., 2007). Outcomes are even better when these skill building components, which are rooted in social cognitive theory and the ecological model, are enhanced (Ickovics et al., 2011).

Recent evidence has begun to link social attachment to immune function (Picardi et al., 2013). In a study of women previously exposed to Epstein-Barr virus, Fagundes et al. (2012) found that supportive relationships improve the responsiveness of the immune system and decreases viral expression. Maunder et al (2012) has recently described improved immune functioning in ulcerative colitis patients in the presence of social support. This is an area of research that is still emerging, and the role of social support in immune function has not been well elucidated. There is an interesting new study by Tarr (2012) and colleagues that describes the increased NK cell activity in mice after the introduction of an aggressive intruders into the habitat being shared by three non-aggressive mice. This may be a crucial link describing the impact of environmental violence on immunomodulation.

A new study examining the relationship between HPA activity and social support from their romantic partner during pregnancy by (Giesbrecht et al., 2013), using a sample of 82 low risk women who were evaluated in each trimester, found that increased levels of psychological distress were associated with higher levels of cortisol during all three trimesters, but that the impact of distress on cortisol was significantly moderated by social support. They found that women with strong social support experienced a 50.4% reduction in average effect of distress on cortisol levels, whereas women who had less social support had increased effects of distress on cortisol levels. This is probably the first study to establish a biological mechanism through which social support can buffer the effect of prenatal stress.

Environmental Stressors

Intimate Partner Violence

A known social/environmental trigger that leads to PTB and LBW is intimate partner violence (IPV) especially when it occurs the year before pregnancy or during the pregnancy(Janssen et al., 2003; Shah & Shah, 2010). A recent meta-analysis reported the incidence of IPV exposure in pregnancy to be between 2 and 23% and these women have an increased risk of PTB and LBW (Shah & Shah, 2010). In a study of neuroendocrine parameters in pregnancies exposed to IPV, Talley and partners (Talley, Heitkemper, Chicz-Demet, & Sandman, 2006) found that women exposed to IPV during pregnancy experience much higher levels of stress and anxiety than the unexposed population. Research over several decades has documented a range of poor pregnancy outcomes in women who were in an abusive relationship either currently or recently before the pregnancy from Bullock and McFarlane's seminal study(1989), showing the association of abuse during pregnancy with the delivery of LBW infants to maternal death from homicide (Campbell et al., 2003). Clearly, IPV represents a threat to the exposed woman and her offspring. This threat is social in nature, and reflects both lack of support and potential or actual danger.

Natural and man-made disasters

From the perspective of adaptive reproduction, women who become pregnant soon after a disaster are actually less likely to experience adverse pregnancy outcomes. Due to the reproductive filtering that occurs amongst women trying to get pregnant, only those who are the "heartiest" will actually succeed in conceiving. The physiological restraint of adaptive reproduction will keep those who are less likely to have uneventful

pregnancies from conceiving until such a time as their HPA axis and sympathetic immune response deems the environment safe and adequate for reproducing. If the ability to adaptively reproduce, that is, restrict reproduction to an optimal time has been naturally selected for in the human population, then the least reproductively fit women will not even conceive in the weeks or months immediately following a disaster. Thus the results of studies that include women not yet pregnant at the time of the disaster are skewed towards normal length gestation.

Indeed, the findings related to PTSD in pregnancy surrounding the WTC attacks in 2001 (Engel et al., 2005) seem to contradict the findings of others (Glynn, 2001) by showing that people who experienced PTSD experienced longer gestations, but since this sample included women who were actually the most reproductively fit, this finding is consistent with adaptive reproduction.

Tobacco Use in Pregnancy

Exposure to tobacco may be the most important modifiable risk factor to decrease adverse birth outcomes. Although prenatal smoking rates have dropped significantly in the last 75 years, the most recent review shows that the prevalence of this behavior during pregnancy still stands at approximately 20% in the United States (Cnattingius, 2004). Populations of pregnant smokers have higher incidences of adverse birth outcomes than their non-smoking counterparts, including infant death (Floyd, Rimer, Giovino, Mullen, & Sullivan, 1993; McElroy et al., 2012). Epidemiologic studies indicate there is a relationship between tobacco use and preterm birth (Ahern, Pickett, Selvin, & Abrams, 2003) and reduced fetal growth (Jaddoe et al., 2007; Vahdaninia, Tavafian, & Montazeri,

2008). Emerging evidence indicates that tobacco use during pregnancy significantly alters the cell signaling of the placenta (Chelchowska et al., 2012; Votavova et al., 2012). In pregnant smokers there is less pregnancy-associated plasma protein A produced by the syncytiotrophoblasts of the placenta, and this affects the amount of insulin growth factors I and II levels. Lower levels of all three of these proteins interrupt normal placental functioning and exchange of nutrients between mother and child, which leads to restricted fetal growth (Chelchowska et al., 2012). There is not yet any literature describing the interplay between environmental stress, stress appraisal, tobacco use behavior and neuroimmune regulation in pregnancy.

A large body of work has been published on the effects of prenatal exposure to tobacco across the lifespan. Prenatal nicotine exposure has been linked to visible problems such as childhood obesity (Koshy, Delpisheh, & Brabin, 2011) and to less obvious issues like delayed reaction to sound and other brain processing issues during infancy (Key et al., 2007)

There is a recent study by Wehby, Prater, McCarthy, Castilla, and Murray, (2011) who examined the effects of prenatal tobacco use on neurodevelopment of 1584 children through 24 months of age. This study excluded children who were born prematurely or had LBW. Infant neurodevelopment was measured using the Bayley Infant Neurodevelopmental Screener (BINS) (Aylward, 1995) and tobacco use was measured via retrospective maternal self-report collected in the postpartum period. The rate of tobacco use in the sample was approximately 11%. A unique aspect of this study, which was analyzed using multi-level structural equation modeling, was that in addition to

evaluating smoking on the individual level, the authors created an endogenous smoking construct, based upon the level of smoking reported by all the women in that community who were enrolled in the study. The results indicate that tobacco use during pregnancy has a significant effect on child neurodevelopment in the first 24 months of life. Wehby and colleagues found that this effect was more profound in children from low socioeconomic background, and this difference could not be entirely attributed to increased rates of smoking in this sub-population.

Previous studies have shown that there is considerable variation in smoking behavior across gestation (Pickett, Rathouz, Kasza, Wakschlag, & Wright, 2005). The literature does not yet describe whether or not particular patterns of exposure changes across gestation can influence birth outcomes or by what mechanisms it could achieve these various outcomes.

Adverse Birth Outcomes of Interest

Preterm Birth

Differentiating the stress pathways from the normal allostatic processes during pregnancy can help underline the pathological themes related to PTB, permitting an examination of the ways in which deviations from the norm are examples of adaptive reproduction. Pregnancy itself presents increased demands on the immune system, increasing the allostatic load over the non-pregnant state. The regulation of this physiological state is understood to occur at the level of trophoblastic tissue (Challis et al., 2009).

Response of the maternal-placental HPA axis in abnormal pregnancies

In women who experience PTB, the aforedescribed dampening effect appears to be dysfunctional (Buss et al., 2009; Glynn et al., 2004; Mancuso et al., 2004). Cortisol, a hormone that is usually associated with anti-inflammatory activity, also inhibits release of prostaglandins during pregnancy. In animal models, however, as labor approaches, cortisol acts on amniotic membrane cells to increase production of prostaglandins (Challis et al., 2009). Buss et al. (2009) found that women who deliver prematurely not only have baseline cortisol levels higher than women who deliver at term, but also have a more dramatic response to stress. This alteration in cortisol responsiveness was predictive of PTB. Furthermore, women who experience particularly high levels of CRH early in pregnancy tend to deliver preterm, and those with very low concentrations of CRH are more likely to deliver post-term (McLean et al., 1995). Thus, it seems that hormonal behavior can predict the length of gestation.

Immune cascade in preterm labor

Ultimately, the activation of the maternal-fetal HPA axis is just one of several mechanisms by which stress initiates an inflammatory cascade and primes the placental delivery clock. In addition to CRH, there are other hormones from the sympathetic nervous system that stimulate the immune response: norepinephrine, angiotensin II and antidiuretic hormone (Challis et al., 2009). Several sources cite this immune activation of the inflammatory cascade as the primary actor in the preterm labor event (Challis et al., 2009; Holst & Garnier, 2008; Kramer et al., 2009; Lyon et al., 2010). This inflammation response is regarded as a variable in the PTB equation that can theoretically be managed (Lyon et al., 2010).

Throughout most of a normal gestation, the placenta produces large amounts of progesterone which restrains the humoral immune system responses that would identify the fetus as a foreign invader and subsequently reject it from the body (Challis et al., 2009). Progesterone also dampens the humoral response to infection. At the approach of full term, there is a switch from the systemic humoral response to the cell-mediated immune response. As unbound CRH levels rise, there is a subsequent increase in the production of proinflammatory cytokines and a massive influx of macrophages that act upon the amniotic membranes and the cervix to remodel the tissue, readying it for labor.

However, if there is an exceptionally high allostatic load earlier in pregnancy resulting from an environmental/social insult, the inflammatory response can be activated by infectious or sterile causes which block progesterone production and shift the immune system into cell- mediated mode sooner than normal. The trophoblastic tissue then produces large amounts of proinflammatory cytokines, which leads to PTB. This stress response can be initiated both by an acceleration of the usual non infective process and by inflammation in response to foreign antigens or fetal hypoxia (Kendall & Peebles, 2005).

Genetic polymorphisms

Family history is a risk factor that can explain why some women exposed to high levels of environmental/social stressors during pregnancy experience adverse outcomes while others do not. Advances in medical technology have helped identify immunogenetic variations that account for these trends in families. Various genetic polymorphisms seem to be associated with increased rates of PTB, and women with the

aforedescribed exaggerated response seem to have a hypersensitive immune system (Holst & Garnier, 2008). In contrast, there are genetic polymorphisms in which the immune response is significantly dampened; these are protective and decrease the risk of PTB in response to exposures to stressors (Simhan, 2003). There are also particular genetic expressions in the fetus that have been associated with preterm delivery (Holst & Garnier, 2008). Dolan's meta-analysis (Dolan et al., 2010) identified 15 maternal genes with a total of 22 polymorphisms and 8 fetal genes with 14 polymorphisms, all of which are implicated to some degree in preterm labor and birth. Clearly, there are multiple opportunities for immunogenetic influence on the timing of delivery and it appears that genetic polymorphisms play an important role in determining the allostatic load a particular woman can bear without adverse effects on the pregnancy.

Low Birthweight

Infants who weigh less than 2500 grams at birth are considered to be low birthweight (LBW). These children experience increased morbidity throughout childhood (McCormick, 1985; Powell, Pharoah, & Cooke, 1986; Singh, Kenney, Ghandour, Kogan, & Lu, 2013). Although there is evidence that variations in reactivity to prenatal stressors can explain variations in fetal growth and development (Bergman et al., 2010; Sarkar et al., 2006), unlike the study of the PNI of PTB, the metabolic events that connect stress appraisal with LBW have not yet been elucidated. But stress processes have been linked to LBW after controlling for PTB (Wadhwa, Sandman, Porto, Dunkel Schetter, & Garite, 1993). In a meta-analysis on psychosocial stress and pregnancy outcome, Littleton, Bye, Buck, and Amacker, (2010) showed that birth weight is the

outcome most strongly associated with psychosocial stress in pregnancy, although it explained only 0.5% of the variance in birth weight. The measures used in the evaluated studies included daily hassles (Kanner, Coyne, Schaefer, & Lazarus, 1981), perceived stress (e.g Cohen, Kamarck, & Mermelstein, 1983), life events (e.g. Curry, Burton, & Fields, 1998) and appraised events or composites. The effect sizes ranged from -0.4 to 0.3 which although small, are not unusual in PNI studies. They conclude that psychosocial stress is most likely a co-variate with other environmental, social, psychological or medical factors that lead to adverse birth outcomes.

African American (AA) women seem to be at particular risk for bearing LBW infants. It has been posited that the disproportionate percentage of African American women, who have a LBW babies in comparison to the population at large, (13.3% compared to 6.8%) is related to various stressors, such as socioeconomic differences, and the effects of racism, along with different thresholds for stress appraisal (Giscombé & Lobel, 2005). There is an established relationship between chronic stress, measured as external stressors, enhancers or buffers of stress and perceived stress during pregnancy and LBW (Borders, Grobman, Amsden, & Holl, 2007). This study examined chronic stress by measuring ease of access to health care, living with a child with a chronic illness, unemployment, crowded living conditions, stressful life events, home hardship and food instability. Interestingly, while hunger is certainly an extreme stress, it could also be a confounder; restricted caloric intake is known to also lead to LBW babies. This has been demonstrated in rats (Mayeur et al., 2013; van Marthens, 1977).

Biomarkers of Interest

The biomarkers in this study were derived from salivary samples. It is only recently that saliva has been recognized as a potential easily obtained source of biomarkers. The salivary fluid is derived from local vasculature which branches from the carotid artery. It is viewed as a source that is therefore reflective of the molecules found in systemic circulation (Miller et al., 2010).

Measures of Tobacco Use

By using biomarkers to measure tobacco use, it is possible to reduce the under-reporting bias that is inherent in self-reports. Accurate disclosure of tobacco use with self-report measures has ranged from 27-95% in a group of studies evaluated by Pickett and colleagues (Pickett et al., 2005), and in a more recent study the rate was 96% in accurate report by non-smokers (Aagaard-Tillery et al., 2010). It appears that combining biomarker measurement with self-reports may give the best measure of overall exposure to tobacco (Dukic, Niessner, Benowitz, Hans, & Wakschlag, 2007). The disadvantage of biomarker measurement to assess amount of exposure is that these measurements only indicate recent use, and cannot account for cumulative dose.

Cotinine

Cotinine (COT) is the major metabolite produced when nicotine (NIC) is metabolized by the liver. All tobacco products contain NIC. Of the chemicals available to measure tobacco use and/or exposure in humans, nicotine and cotinine are the two that are highly sensitive and specific (Benowitz, 1999). Bioassay measurements of NIC correlate to exposure within several hours prior to sampling (Benowitz, 1996). COT can be measured in saliva, serum and urine in women who are actively smoking and in those

who are passively exposed to tobacco smoke and reflects exposure within the previous 1-4 days (Benowitz, 1996). Benowitz and Jacob (1994) established that outside of pregnancy, COT has a half-life of about 17 hours. However, COT appears to be metabolized and eliminated almost twice as fast during pregnancy than usual; the half-life is reduced to about 9 hours (Benowitz & Jacob, 1994; Dempsey, Jacob, & Benowitz, 2002). Thus COT measurement reflects less than an entire days' cigarette use. Nevertheless, cotinine has long been established as a valid predictor of pregnancy outcome (Li, Windsor, Perkins, Goldenberg, & Lowe, 1993; Mathai, Skinner, Lawton, & Weindling, 1990).

Diet, gender, age and pregnancy are just a few of the variables that affect nicotine metabolism (Hukkanen, Jacob, & Benowitz, 2005). The concentrations of Cytochrome P450 2A6 (CYP2A6), the enzyme primarily responsible for oxidizing NIC and COT, appears to be the cell-signaling factor involved in these variations. Benowitz's group hypothesizes that CYP2A6 may be synthesized in much larger amounts than usual during pregnancy, and may actually be produced by the placenta as well as the liver (Dempsey et al., 2002).

When measuring COT levels, there is an expected variation in amounts of COT present in different body fluids because of variations among subjects in both percentage of NIC converted into COT, and in differences in metabolic clearance (Benowitz & Jacob, 1994). While this raises concerns about the usefulness of these measurements, it is interesting to note that the inter-subject and between subject variability seen in NIC and

COT levels after tobacco exposure is consistent with or less than the variation seen in the metabolism measurement of many other drugs (Levy, Ebling, & Forrest, 1994).

In a repeated measures comparison between pregnancy and postpartum, one study has shown that during pregnancy, NIC is cleared 60 percent faster and COT metabolized 140% faster compared to the postpartum measurements (Dempsey et al., 2002). This validated the earlier work of Rebagliato and colleagues (Rebagliato et al., 1998) that demonstrated lower salivary cotinine levels of 3.5ng/ml per cigarette in pregnancy versus a rate of 9.9ng/ml per cigarette measured in the same population during the postpartum period.

In a recent study, Fang, Johnson, Stopp, and Espy (2011) identified three categories of smoking exposure (none, low-exposure, high-exposure) through analysis of a construct which included the Fagerstrom nicotine dependence scores, cigarette brand, tobacco self-report, maternal and newborn urine COT levels, which are predictive of birth weight, and neonatal irritability.

Secondary Data Analysis

The datasets for the secondary analysis proposed for this dissertation, "Baby BEEP" (R01 NR05313-03) that evaluated the efficacy of a smoking cessation intervention for pregnant women and its mother/infant dyad follow-up "Baby BEEP for Kids" (R01 HD045542) will be described in detail in Chapter 3. However, several of the limitations and advantages of this particular dataset are described in this section, along with a discussion of the general limitations and advantages of utilizing secondary data for research.

Limitations

While existing datasets may provide unique opportunities to examine issues that have not previously been studied, they do present some significant limitations which need to be acknowledged. Not all the constructs posited as important in the prenatal stress process literature have composite measures included in the proposed datasets. This includes variables such as medical conditions, alcohol use, medicine ingested, nutrition or exercise. The dataset does not contain community level data. These missing variables constitute an omitted variable bias.

There are several limitations to the particular datasets proposed in chapter three. The sample is from an all rural study population with very little ethnic diversity, and no control group of pregnant non-smokers. While this may raise concerns about the generalizability of the study findings to non-Caucasians, given that African Americans have higher than average rate of preterm births (Keppel, Pearcy, & Wagener, 2002; O'Campo et al., 2008; Partridge, Balayla, Holcroft, & Abenhaim, 2012; S. Zhang et al., 2012) and LBW (Collins & David, 2009; Kleinman & Kessel, 1987; Rosenthal & Lobel, 2011), the homogeneity in this sample controls for epigenetic differences that could confound timing issues.

In addition, there are two "missing data" issues, one potential, and one real. Because women were enrolled at different gestational ages, it may not appropriately reflect rates of early pregnancy loss in this population, meaning that gestational length in the study may not be representative of average length of gestation. However, the rate of

miscarriage in the enrolled population can be compared to the general population, and inferences made based upon those similarities or differences.

Advantages

It makes sense to use secondary data for this dissertation project for several reasons. The economy of time and effort is an obvious advantage. Secondary data analysis allows for an initial evaluation of this theoretical model that will improve our understanding of the relationships between these phenomena and identify weaknesses. This will insure that future studies that involve primary data collection will be more refined and the more precise than would otherwise be possible.

Summary

There is considerable literature that links prenatal mood, psychosocial stress and social support processes with birth outcomes. As this review has shown, the timing and cell-signaling involved in these relationships has not yet been well-elucidated. Employing the ultimate theory of adaptive reproduction and the proximal theoretical framework of psychoneuroimmunology to stress and mood research in pregnancy provides opportunities to not only clarify underlying mechanisms but also to improve prenatal care.

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Chapter 3: Research Methods

Introduction

The long-term goal of this research trajectory is to operationalize and test the theoretical model of adaptive reproduction in order to develop interventions to improve birth outcomes. This involves understanding the relationship between environmental stressors and psychoneuroimmune changes that lead to adverse birth outcomes (see Figure 3.1). The specific objective of this proposal is to test this theoretical model of adaptation in pregnancy using BabyBEEP data. This undertaking will include evaluating the presence and timing of relationships between intimate partner violence (IPV), tobacco use, psychological variables, social support and neuroimmune changes during pregnancy as they relate to gestational length and birthweight outcomes. Intimate partner violence has been associated with premature birth (occurring at less than 37 completed weeks gestation) and infants being born small for gestational age (SGA), which is weighing below the 10th percentile for their gestational age (Shah & Shah, 2010). Tobacco use has also consistently been linked to premature birth and low birthweight (less than 2500 grams at birth) (e.g. Floyd, Rimer, Giovino, Mullen, & Sullivan, 1993; Jaddoe et al., 2007; McElroy et al., 2012), thus it will be treated as a covariate in this research. The central hypothesis, based upon work of Challis (1995) and McLean and colleagues (1995), is that due to evolving placental physiology, the impact of stress, depression, tobacco use and social support on adverse birth outcomes will vary across the gestation.

This hypothesis has been formulated, in part, based upon data in non-human animal populations with similar social structures (e.g. Kaplan, 2004; Wasser & Barash, 1983), and data suggesting that stress exposure leads to "priming of the placental clock" (Challis, 1995; McLean et al., 1995). An additional hypothesis is that IPV in the perinatal period (during or in the year before birth) will change the timing of the impact of other stress, mood and social support on birth outcomes. The rationale for the proposed research is that once the timing, phenotypic and neuroimmune propensity to deviate from normal reproductive trajectory due to environmental stressors is understood, it will be possible for perinatal health care professionals to tailor more effective and efficient interventions aimed at ameliorating poor outcomes.

This is a quantitative study using secondary data analysis that utilizes psychosocial instruments and biomarker data that will be analyzed using structural equation modeling (SEM).

Research Question and Hypotheses

This project utilizes secondary data analysis of a sample described in the following section to address the following research question: Are different levels of stress, depression, social support at any particular month of pregnancy more highly associated with gestational length or birthweight after controlling for tobacco use?

The hypotheses and specific aims are as follows:

Hypothesis #1

The impact of stress, depression, social support and tobacco use on adverse birth outcomes varies across gestational time periods.

Hypothesis #2

The pattern of impact of stress, depression, social support and tobacco use on adverse birth outcomes will vary in different patterns for women who experience IPV in the year before or during pregnancy compared to women who are not currently experiencing IPV.

Specific Aim #1

To identify the latent variables in the BabyBEEP dataset relating to stress, depression, anxiety and social support

Specific Aim # 2

To determine the linearity of the relationship among tobacco use and the latent constructs of stress, depression, and social support over time.

Specific Aim #3

Determine the differences in patterns of stress, depression, tobacco use and social support impact across time on gestational length and birthweight in pregnancies exposed to abuse compared to those not exposed to abuse:

c. Determine the association of tobacco use and the latent variables (social support, stress, and depression) at different gestational ages.

d. Determine the impact of the latent variables on gestational length and birthweight after controlling for tobacco use during pregnancy.

Sample

This is a secondary data analysis performed on data that was collected through an R01 NR05313 to evaluate the efficacy of a smoking cessation intervention for pregnant women (N=695). The original study was approved by the IRB at the University of Missouri, and was conducted between 2002 and 2006 in 21 counties in rural Missouri. This sample was comprised of pregnant women who were smoking at least 1 cigarette a day upon enrollment.

Inclusion and Exclusion Criteria

To be eligible for the study the women had to be at least 18 years of age, and less than 24 weeks pregnant based on last menstrual period. They also had to speak English, have access to a telephone and report smoking at least 1 cigarette or more per day. The tobacco use self-reports were confirmed with baseline cotinine measurements of at least 30 ng/ml. Women who were less than 18 years of age, and/or had stopped smoking prior to study enrollment, or had cotinine levels below 30 ng/ml, were excluded from this study.

Minority inclusion

The population in the area of central Missouri in which the study was conducted is largely Caucasian. Reflecting geographic population demographics, only 3.5% of the population was African-American and other ethnic groups were even less represented (Table 4.1). This homogenous ethnic sample is a strength of the study; epigenetic differences in ethnic groups are not confounding the results.

Setting

Women were recruited from WIC clinics in central Missouri. Eligibility for enrollment in these clinics is set at 185% of the poverty level and below. Women attending these clinics were thought to be exposed to a larger number of environmental stressors than women with higher socioeconomic status.

Original BABYBEEP Study Methodology

The original study was a randomized controlled trial that utilized 2 x 2 repeated measures factorial design with two levels of education intervention (Present or Absent) and two levels of telephone social support (Present or Absent). Thus the study had four treatment groups:

1. Combination group, which received both the nurse-delivered telephone social support and an established educational smoking cessation program for pregnant women.
2. Telephone group, which received only nurse-delivered telephone social support.
3. Education group, which received only the established educational smoking cessation program for pregnant women.
4. Control group, which received only usual prenatal care, and no study intervention.

Women in the Combination and Telephone groups received weekly phone calls from a support nurse. Women in the Combination and Education groups participated in an educational program called “Stop Smoking! A Special Program for Pregnant Women”

which had been adapted from materials developed by the Maxicare Research and Educational Foundation with funding provided by the Division of Lung Diseases-National Heart, Lung and Blood Institute; the University of Texas School of Public Health and the Agency for Health Care Policy and Research. It consisted of eight booklets (booklet 1, "A Turning Point", booklet 2, "Taking the First Step", booklet 3, "Seeing patterns in your smoking"; booklet 4, "Stopping gradually or going 'cold turkey'"; booklet 5, "Ready, Set, Quit"; booklet 6, "Staying alert"; booklet 7, "Stopped for good"; and booklet 8, "A Non-smoking lifestyle"), which were mailed one at a time to participants across eight consecutive weeks.

Original Study Data Collection

The following four instruments were administered by registered nurses to each participant at three gestational ages: at enrollment; during late second trimester or early third trimester, and at the end of the pregnancy. The following instruments were included in this secondary analysis: Cohen's Stress Index (Cohen, Kamarck, & Mermelstein, 1983); the Prenatal Psychosocial Profile (PPP) (Curry, Campbell, & Christian, 1994), which measured stress, social support and self-esteem; the Mental Health Screening Test (MHI-5) (Ware, Snow, Kosinski, & Gandek, 1993) and the Abuse Assessment Screen (AAS)(McFarlane, Parker, Soeken, & Bullock, 1992), which is a screen for IPV. In addition, all women had cotinine levels were measured monthly throughout the original BabyBeep study.

Instruments.

Independent variables.

The **Perceived Stress Scale** is a 4-item instrument which is meant to assess general feelings of stress in situations, when longer instruments are inappropriate, such as telephone interviews. It has a 5-point Likert ranking scale and a reliability coefficient in the original evaluation of .72, with test retest reliability of .55 at time points 2 months apart (Cohen et al., 1983). The PSS score is calculated by reverse scoring the second and third questions and summing the totals, with higher scores indicating more perceived stress.

The **Prenatal Psychosocial Profile** (PPP) is a 44-item symmetrical likert-type scale comprised of: (1) a unique stress measurement tool developed by Curry, Campbell and Christian (1994), (2) the shortened version of Brown's Support Behaviors Inventory (SBI, Brown, 1986) and (3) Rosenberg's Self-Esteem Scale (SES, Rosenberg, 1965). The internal consistency for the PPP was established by Curry et al. (1994) using a sample of 3,444 pregnant women of all ages in rural and urban settings across the United States, collected in five separate studies. The reliability coefficient has been established at the 0.89 level for pregnant women, exceeding Nunnally & Bernstein's (1994) criteria of 0.80 for reliability. Validity has been well established (Curry et al 1994; 1998).

The PPP stress subscale, PPP Partner Support subscale (PPP-PS) and the PPP Other Support subscale (PPP-OS) are each scored by summing the 11 items, with higher scores indicating more stress or social support respectively. In order to score the PPP self-esteem subscale, reverse scores 6 of the 11 questions (A20A, A20B, A20D, A20F, A20G, and A20K) and sums these with the remaining 5 questions. Increased self-esteem is associated with higher scores.

The **Mental Health Screening Test** (MHI-5) is a five item self-report instrument to evaluate depression which is also known as the mental health subscale of the 36-item Short-Form Health Survey (Ware et al., 1993). It uses a likert scale (ranging from 1 "all the time" to 6 "none of the time") to evaluate anxiety, depression, loss of behavioral/emotional control, and two items related to psychological well-being. This instrument has good criterion related validity against the Beck Depression Inventory (van den Beukel et al., 2012).

The MHI-5 score is calculated by reverse scoring second and fourth items, then summing the five items. The score is then calculated with the following formula: $\frac{(sum\ of\ scores-5)}{25}\ x\ 100 = MHI\ mental\ health\ score.$ Higher scores are indicative of increased mental health.

The **Abuse Assessment Screen** (AAS) is a five item self-report measure that screens for physical, sexual and emotional abuse during the woman's lifetime, within the past year, and during pregnancy and whether the woman is afraid of her partner or anyone else. It is a well-validated tool developed by the Nursing Research Consortium on Violence and Abuse (Bhandari, Bullock, Anderson, Danis, & Sharps, 2011; McFarlane et al., 1992).

The first question of the AAS evaluates past abuse. The second, third and fourth questions all pertain to physical or sexual abuse occurring currently or within the year before pregnancy. Any positive response to any of these three questions at any of the three data collection sessions became a positive response to this category. The final question asks, "Are you afraid of your partner or anyone else"

Biomarker data.

Cotinine is the most common metabolite of nicotine found in humans (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987) and has become a standard biomarker used to measure tobacco exposure in humans (Dukic, Niessner, Benowitz, Hans, & Wakschlag, 2007; Hukkanen, Jacob, & Benowitz, 2005; Jarvis et al., 1987). The half-life of this metabolite is approximately 15 hours (Jarvis, Russell, Benowitz, & Feyerabend, 1988). Saliva samples were acquired at baseline and at monthly intervals throughout the pregnancy. In the BabyBEEP study the saliva samples were collected according to a protocol established by the Clinical Pharmacology Laboratory at the University of California at San Francisco. In this protocol, the women chewed a piece of Parafilm to stimulate saliva production, and 5-10 ml of saliva could then be collected, immediately placed on ice, and then stored at -20 C when the research nurse returned to the office from the home visit.

Dependent variables.

The outcome variables of interest in this new study are gestational length and birthweight.

Gestational length is measured as the **estimated gestational age at delivery** (EGA). It was recorded by subject self-report, as was infant birthweight, which was recorded in pounds and ounces and had to be converted to **grams** for the analysis. Self-report of EGA could potentially compromise the validity of the results. Theoretically the same concern about self-report exists for birthweight, however, women are told their babies birthweight at delivery, but not told their accurate gestational age upon admission

to the hospital. It is more likely that they will provide accurate answers for birthweight than for EGA. Nevertheless, the decision was made to utilize self-report of EGA as the most accurate available dating for the length of gestation rather than calculating the gestation length from reported last menstrual period and birthdate, because it was believed to be more accurate than women's recollection of their last menstrual period.

A total of 636 women completed the third interview for this study (a 93% retention rate) providing gestational length for all pregnancies, and birthweights for the 627 that were born after 21 weeks gestation. The presence of these outcomes in the data set is strength for this study.

Model Development Procedure

The procedures for model and data preparation, model evaluation are presented here. The procedures are discussed in three sections: 1) Theoretical model development 2) Data restructuring for secondary analysis and 3) Power Analysis.

Theoretical Model Development

The theoretical explanatory model was developed based upon the Adaptive Reproduction framework and an extensive review of the literature on determinants of low birthweight, and gestational length discussed in Chapter 2. A theoretical model was developed (see Figure 2.1) that stipulates the relationships between the explanatory variables and outcomes.

The *Broad Psycho-Social Context*, as described in Chapter 2, refers to the overall health and adaptability of the entire community. This encompasses the physical and social setting in which people live, including culture, socioeconomic environment. Issues

such as safety and access to resources such as food, water, adequate housing, and opportunities for education, meaningful work or work that provides a living wage and intact social structures are all included within the broad psychosocial context. In the BabyBEEP data set, all participants came from a broad psycho-social context that was rural and poor. A qualitative study of the lived experience of demographically similar abused women from the same geographical area found that violence and social chaos from housing and employment instability was ubiquitous in these women's broad environment (Burnett et al., 2013).

This broad environment influences both the *Psychoneurological Context* (mental health state), which will be measured in this study as a combination of stress appraisal and mood, and the *Nuclear Social-Behavioral Context* (an individual's immediately available social resources, surroundings and current behaviors), modeled via tobacco use and social support in this current study. *Placental Cell Signaling* is influenced by both *Psychoneurological Context* and *Nuclear Social-Behavioral Context.* These placental processes mediate the relationships between *Psychoneurological Context* and *Nuclear Social-Behavioral Context* and *Reproductive Outcomes.*

Data regarding variables included in this framework exist for multiple time points in pregnancy from 4 weeks gestation through 41 weeks. This allows modeling to evaluate how these explanatory variables may impact outcomes differently due to the ever-evolving physiologic mileau of pregnancy (specifically the changing patterns and processes of placental cell signaling). The evolving production of progesterone across gestation is depicted and demonstrates this changing physiologic mileau reflected in the

arrangement of specific gestational time periods (see Figure 3.1) that are used in the full structural equation model (see Figures 3.2 and 3.3).

Data Restructuring for Secondary Analysis

Both variables and cases from the BabyBEEP dataset were restructured in order to evaluate the model for Adaptive Reproduction. The process and rationale for this restructuring is described below.

Gestational time period groups.

The data BabyBEEP data set is restructured so that each subject's data will be evaluated according to the specific gestational age time period during which it was collected. The specific gestational ages at data collection varied from woman to woman. The conceptual model depicted in Figure 2.1 is being evaluated at seven gestational time periods (see Table 3.1).

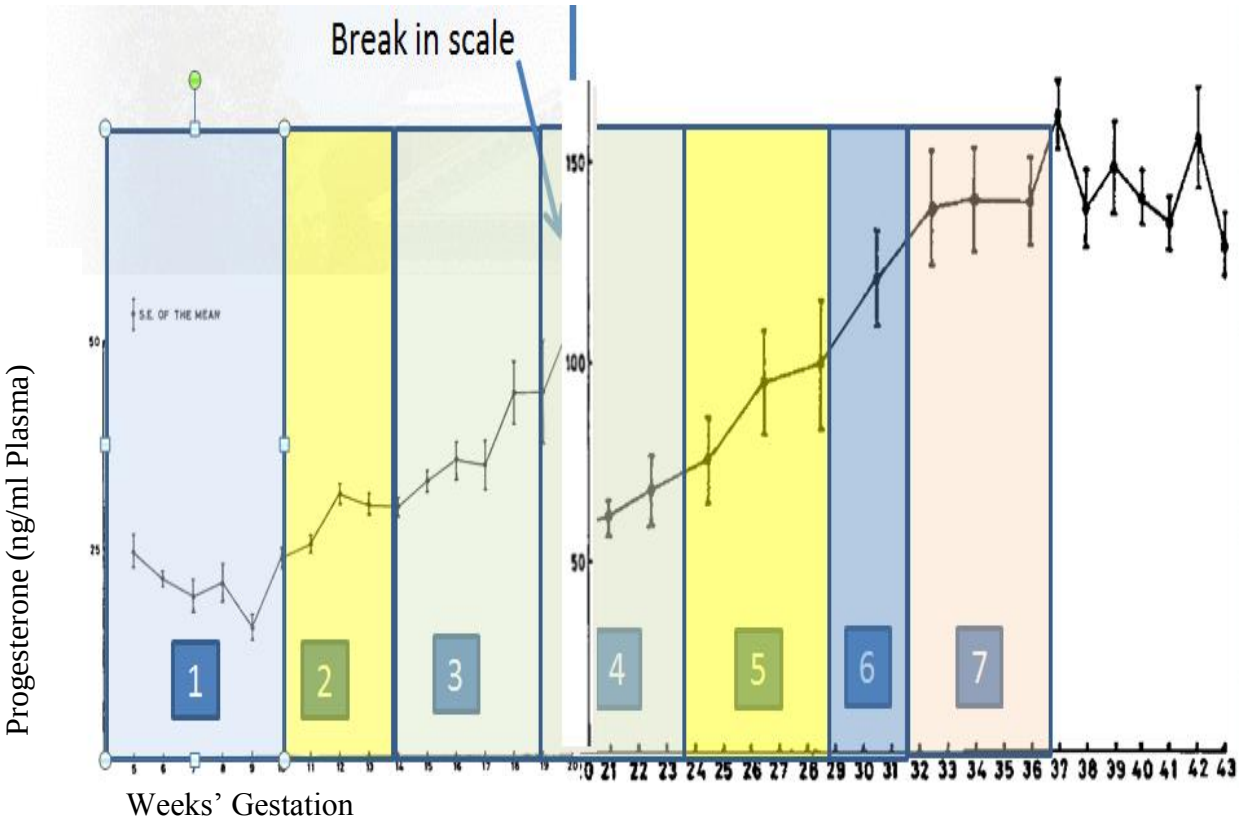

Figure 3.1: Progesterone levels in human pregnancy. Numbers on graph represent the different gestational time periods being assessed in this study. Adapted from Johansson, E.D. (1969) Plasma levels of progesterone in pregnancy measured by a rapid competitive protein binding technique. p.612.

Table 3.1

Gestational Ages for each Group Time Period

Gestational Age	Group Number	N
4-9 weeks	1	128
10-13 weeks	2	236
14-18 weeks	3	195
19-23 weeks	4	128
24-28 weeks	5	160
29-31 weeks	6	300
32-36 weeks	7	147

The cut-off points for each gestational time period are based on either placental physiology, observed changes in the immune mileau of pregnancy described in the literature, or constraints of the dataset. There are 13 cases in the BabyBEEP dataset in which data was collected between 37 and 41 weeks EGA. The decision to exclude the data collected at that late gestational age from analysis was based upon concerns about both the generalizability of results from such a small sample and concerns that it could make it harder for the entire model to converge during path analysis.

The physiologic considerations involved in the determination of these time periods derive principally from the shifting availability of placental interfaces and hormonal changes throughout gestation. There is a major alteration in placental physiology at the completion of nine weeks EGA. Prior to this stage, it is the extravillous syncytiotrophoblasts that provide the primary cell signaling contact between the pregnancy and the maternal system (Borzychowski, Croy, Chan, Redman, & Sargent, 2005). The changing physiology of the placenta is well represented by examining progesterone production during the pregnancy (see Figure 3.1). After the luteal-placental shift in production of progesterone around the tenth week of pregnancy, the placenta produces ever increasing amounts of progesterone throughout the remainder of gestation (Johansson, 1969). Progesterone is a hormone associated with maintenance of the pregnancy; therapeutic administration of this hormone throughout pregnancy has been linked to longer gestations and higher birthweights (Di Renzo, Mattei, Gojnic, & Gerli, 2005).

In addition, there are other immune changes that occur at specific stages of pregnancy. At the beginning of the second trimester both circulating Natural Killer cell numbers (specifically $CD56^{bright}$) and Natural Killer T cells (NKT) increase (Sargent, Borzychowski, & Redman, 2006). These cells orchestrate significant cell signaling throughout pregnancy.

The immunomodulation that occurs at the beginning of the third trimester is so remarkable that the activity has been compared to sepsis (Sacks, Studena, Sargent, & Redman, 1998).

Restructuring of the data into seven gestational time periods, was performed using *IBM SPSS Statistics for Windows* (2013). The original BabyBEEP interviews were identified by color; the first interview was YELLOW, the second interview was BLUE and the third (postpartum) interview was GREEN. These colors are used to refer to the original study interview times as the restructuring of the data is described. The YELLOW and BLUE (antepartum) interview data was recategorized using the EGA data to assign a gestational group based upon the schema described in Table 3.1. The manifest variables of interest were then reassigned according to group membership, so that when the YELLOW and BLUE interviews were merged into one dataset, interview data from all time points were represented on one line.

Operationalizing of Variables

The operationalization of the theoretical model is significantly constrained by the variables that exist in the BabyBEEP dataset. The measurement instruments for the entire set of variables involved in the structural equation model along with their

theoretical and operational definitions are described in Table 3.2. The following discussion describes the decision-making regarding the construction of latent variables which were used in the analytic model.

Social support construct

There is not a single, definitive multidimensional definition for the concept of social support (Williams, Barclay, & Schmied, 2004). One classic approach, described by House (1981), has been to envision 4 components comprising social support: an emotional factor that includes esteem, trust, listening, and affection; an element of appraisal, which includes both feedback and affirmation; an informational aspect that provides advice and coaching; and an instrumental component that describes the provision of physical resources, or human capital in the form of labor resources.

For this study, the latent construct of social support will be comprised of the two social support subscales from the PPP which examine sources of support (the partner and other family/friends) separately. Women are asked to rate their level of satisfaction with the support they receive from their partner and then the scale is repeated to measure their satisfaction with support received from others (family or friends). These subscales are more heavily weighted towards the emotional aspects of social support described by House (1991), with five questions out of 11 addressing this aspect (Items A,D,F, H, & I). Two of the questions address support as forms of appraisal (Items B & G), and only one question addresses informational type supports (Item J). The issue of instrumental support is addressed by the remaining three items (C, E & K) of the subscales. Although there may be value for other purposes, in examining the construct loadings to these four

aspects of social support, because of the researcher's specific interest in social support provided by others, especially in the context of abuse, the decision was made to evaluate the loadings to the source of the support, partner versus other.

Depression construct

The theoretical definition of depression for this study is, an "unpleasant, but not necessarily irrational or pathological, mood state characterized by sadness, despair, or discouragement; "the blues"; (that) may also involve low self-esteem,"(U.S. National Library of Medicine, 2013). The caveat about low self-esteem at the end of that definition, combined with the language of despair, leads to the inclusion of two manifest variables in the construction of this construct. The first variable is the calculated total score of the MHI-5, a validated tool for diagnosing depressive symptomology clinically. But two items from the Rosenberg's self-esteem scale are also utilized as an indexed variable specifically to capture the feelings of despair and worthlessness that are not explored in the MHI-5, but might have some bearing on the outcomes related to depression within an Adaptive Reproduction framework. Wasser and Barash (1983) have suggested that the perception of personal fitness for reproduction may influence the chance of reproductive success in animals, and feelings of worthlessness or uselessness could be construed as relating to personal fitness for any task.

Stress construct

One of the difficulties in designing this type of construct is that in general, in regard to the psychological instruments currently in use to measure stress during pregnancy and its impact on birth outcomes, the underlying theoretical assumptions have

been largely undocumented (Alderdice, Lynn, & Lobel, 2012). Lobel's research group suggests that there are basically three components of stress to be measured; environmental stressors, psychological appraisal of stressors and the woman's emotional response (Wadhwa et al., 2011). Typically clinical studies have only reported one of these measures, or in some cases two.

Table 3.2

Theoretical and Operational Definitions of Study Variables and Measurement Instruments

Latent Constructs	**Theoretical definition**	**Operational definition**	**Measurement Instrument**
Independent Variables			
Nuclear Social-Behavioral Context	An individual's immediately available social resources, surroundings and current behaviors	Theoretically loads to Social Support and Tobacco Use	Instruments described below:
Current Abuse	Abuse (physical or sexual) that has recently occurred or is ongoing.	Physical or sexual abuse occurring in the year before pregnancy or currently	Abuse Assessment Screen (AAS) (McFarlane et al., 1992) Questions 2- 4: Any positive response to any of these three questions at any of the three data collection sessions became a positive response to this category as described below: AAS 1-4 were summed on both sheets (Yellow and Blue) IF (Yellow_Current_Abuse ≠ 0 or Blue_Current_Abuse ≠ 0 or Green_CurrentAB ≠0) Current_Abuse_Final=1. EXECUTE. Then Add "0" for "Current_Abuse_Final" , meaning that if yellow, blue or green is 0 and no other values are >0 then Current_Abuse_Final=0. b

Latent Constructs	Theoretical definition	Operational definition	Measurement Instrument
Independent Variables			
Social Support	Social support consists of 4 components: Emotional (e.g. esteem, trust, listening, and affection); appraisal (e.g. feedback and affirmation); informational (e.g. advice) and instrumental (physical resources, labor resources) support. (House, 1981)	Latent Construct loading to: • the 11 item "partner support" and • 11 item "other person support" subscales of the PPP (Curry et al., 1994) which are both based on Brown's, (1986) Support behavior inventory. *Continuous variable*	**Prenatal Psychosocial Profile (PPP)** 22 items from the two social support subscales (from BB.IntrvwDataRcrd.071206 .FINAL(1).xls: Manifest variable #1:Partner Support: the partner support variable was the sum of A19A-K, Excel code: =SUM(AC4:AM4) Manifest variable #2: Other support: the sum of PPP other person support scale (A19AOP-KOP.)
Tobacco Use	Consumption of tobacco.	Loads to Cotinine level and Self-report of tobacco use *Continuous variable*	Measured by **Salimetrics** kits found in BB.FINAL.SALIVA.Sampl esRcrd.072107(1).xls; gestational ages assigned based on date and estimated due date at initial interview or if second interview had already occurred and due date had been adjusted, the more recent date was utilized for calculation of gestational age. When two measurements occurred in one group, the case was dropped from that timepoint. These were grand mean -centered for means plotting and then the original values were standardized for model measurement.
Psycho-neurological Context Constructs	Affective state and appraisals responsivity to the environment.	Theoretically loads to Depression, Stress *Continuous variables*	Instruments described below:
Depression	An "unpleasant, but not necessarily irrational or	A latent construct that loads to MHI-5 calculated	From database: BB.IntrvwDataRcrd.071206

Latent Constructs	Theoretical definition	Operational definition	Measurement Instrument
Independent Variables			
	pathological, mood state characterized by sadness, despair, or discouragement; "the blues"; may also involve low self-esteem,"(U.S. National Library of Medicine, 2013)	total score and A20I "feels useless" and A20J "at times think you are no good at all" from the PPP Self-esteem subscale.	.FINAL(1).xls: The first manifest variable is the calculated score from the Mental Health Index-5. **MHI-5-** uses a likert scale (ranging from 1 "all the time" to 6 "none of the time") to evaluate anxiety, depression, loss of behavioral/emotional control, and two items related to psychological well-being. (Ware, Snow, Kosinski, & Gandek, 1993) Scoring of this instrument is meant to proceed as follows: MH2 and MH 4 are both reverse scored and these results added to the sums of MH1, MH3 and MH5. After subtracting by 5 this sum is divided by 25 and then multiplied by 100. 65 is considered a cutoff correlating to depressive symptoms (Rumpf, Meyer, Hapke, & John, 2001) . In this study, the scoring was reversed, so that higher scores correlated with depressive symptoms, as follows: MH1,MH3 and MH5 were reverse coded and added to the sums of MH2 and MH4. After subtracting by 5, this sum is divided by 25 and the multiplied by 100. This aligns the negative outcome of depression with higher stress scores for comparison purposes. The second manifest variable for this construct is the sum of two items reverse scored from the **PPP**

Latent Constructs	Theoretical definition	Operational definition	Measurement Instrument
Independent Variables			
			self-esteem scale: A20I- "Feels useless at times" A20J "at times think you are no good at all". Both of these variables, Appraisal and Perceived Stress/Anxiety were grand mean centered for means plots, and standardized for modeling purposes.
Stress	A physiologic response to environmental threats or demands (Cohen, Kessler, & Underwood, 1995). This has three measureable components: external stressors themselves(measured elsewhere in the model), appraisal of stress and emotional response (Wadhwa, Entringer, Buss, & Lu, 2011). Anxiety is an emotional response/experience characterized by worry and emotionality (Spielberger, 1980)	Latent construct loading to • Appraisal of stressors • Perceived Stress/Anxiety	Two manifest variables were constructed from variables in the database: BB.IntrvwDataRcrd.071206.FINAL(1).xls: 1. Appraisal of stressors: PPP-11 item stress subscale total score (Curry et al., 1994) This was the sum of A18A-A18K. 2. Perceived Stress/Anxiety: This is the sum of questions from three different measures in the BabyBEEP dataset: a. Cohen's PSS-4 item scale total score. To calculate this C2 and C3 are reverse scored, then summed with C1 and C4. (Cohen, Kamarck, & Mermelstein, 1983). b. The sum of two questions on MHI-5 that specifically address worry and emotionality: MHI-5 #1 –"how much are you nervous" MHI-5-2 reverse scored

Latent Constructs	Theoretical definition	Operational definition	Measurement Instrument
Independent Variables			
			"how much have you felt calm and peaceful?" c. Question AAS5 "are you afraid of your partner or anyone else" Both of these variables, Appraisal and Perceived Stress/Anxiety were grand mean centered for means plots, and group mean centered for modeling purposes.
Dependent variables			
Gestational Length	The amount of time an embryo or fetus remains in the uterus	Estimated Gestational Age (EGA) at birth calculated by counting forward from the first day of the woman's last menstrual period to the actual date of birth, OR counting forwards or backwards from the Estimated Due Date (which is 40 weeks EGA) to the date of birth. *Continuous variable*	From dataset : BB.T3.BirthDataSet.Org.BB.ALL(1).xls EGA at birth was captured by participant self-report at the third data interview (the initial postpartum data collection point) in the original study. The variable is called Gest Age.
Birthweight	The baby's weight at birth.	Weight at birth measured in grams. *Continuous variable*	From dataset : BB.T3.BirthDataSet.Org.BB.ALL(1).xls, this was collected by mother's self-report at initial postpartum data collection. The variables D13 lb and D13 oz were both converted to grams and summed, then mean centered.

To make the modeling of stress in this study as comprehensive as possible, ideally all three types of stress measurement would be included. The motivation for this stems from Dunkel-Schetter and Glynn's (2010) review of psychological stress instrument research relating to preterm birth, in which studies were evaluated according to type of

stress measurement utilized: groups that included environmental stressors (usually an earthquake, flood or terrorist act); the appraisal of stress was labeled perceived strain from life events; and finally scales that measured emotional response were labeled perceived stress scales. Environmental stressors alone were associated with PTB in 15 out of 22 studies in the Dunkel-Schetter and Glynn review. Twelve out of 18 studies on strain or stress of life events showed an association with PTB in this review. And these authors found perceived stress was related to PTB in only 5 out of 12 studie. No particular type of measure consistently demonstrated association between stress and preterm birth across studies. Perhaps utilizing the three types of measurement in one study will yield a more powerful and consistent effect.

Accordingly, the stress construct proposed for this model consists of two manifest variables reflecting two of the types of stress measurements: an appraisal scale and an emotional response item. Appraisal and emotional response are both aspects of *psychoneurological context*. The best measure of stress appraisal available in the dataset consists of the PPP stress subscale. This subscale has been used to model perceived stress. The PPP stress subscale represents an appraisal measure of life stress or strain, by asking, "to what extent do the following items cause you stress or hassle". A composite variable utilizing Cohen's PSS-4 score, two of the questions in the MHI-5 evaluate a person's emotional state, and the response to question 5 on the AAS "Are you afraid of your partner or anyone else" is the measure of emotional response to stress in the model.

The third component of stress, environmental stressors, is included in the overall model group comparison. The two groups that are compared are 1) those currently or

within the last year exposed to abuse, which is an environmental stressor, and 2) those who were not currently exposed to abuse. The question of whether abuse is a confounder or an explanatory covariate with a place in the model, is legitimate. Honoring the theoretical assumption that the psychoneuroimmune cell signaling at the level of the placenta is different in women experiencing abuse is different, the issue was resolved in favor of using abuse as an overall grouping variable, to look at WHEN these theoretical differences seem to be occurring.

Data Preparation

Two databases were renamed, restructured and merged in order to create the dataset that was utilized for SEM. Table 3.2 describes the operationalization of the variables from the following databases:

- BB.IntrvwDataRcrd.071206.FINAL(1).xls →Temporal Associations
- BB.FINAL.SALIVA.SamplesRcrd.072107(1).xls→ Cotinine

A summary of the data preparation activities is described in Table 3.3.

Table 3.3

Summary of Data Preparation

Variable Name	Temporal Dataset			Cotinine Dataset	Disaggregated by Gestational Grouping[1]	Grand Mean Centered (Mean)
	Yellow	Blue	Green			
Study ID	X	X	X	X		
EDD	X					
EGA (Gest age)	X	X				
Gest length			X			
D2(parity)						
D10(education)	X					11.350
D14(gender)-not in model			X			
Age	X					23.140
Birth weight			X			
Total Score PPP Stress	X	X			X	20.897
Total Score PPP P Support	X	X			X	45.866
Total Score PPP O Support	X	X			X	51.953
A20 I&J Sum	X	X			X	5.595
MHI5 Calculated Total Score	X	X			X	61.410
PSA	X	X			X	17.956
Current Abuse[3]	X	X	X			
Cotinine				X	X	127.75

Note 1: Gestational Groups: Group 1,EGA 4-9; Group 2 EGA 10-13; Group 3,EGA 14-18; Group 4, EGA 19-23; Group 5,EGA 24-28; Group 6,EGA 29-31; Group 7 EGA 32-36; Group 8, EGA 37+ (Group 8 was eventually removed from final dataset).
Note 2: This variable was summed from Yellow, Blue and Green sheets. If it is an amount greater than zero at any time period, then it needs to be a 1, if it is always zero, it remains zero in the final variable.
Note 3: Constructed by the following process: IF (Yellow_Current_Abuse > 0 or Blue_Current_Abuse > 0 or Green_CurrentAB >0) Current_Abuse_Final=1. EXECUTE. Then Add "0" for "Current_Abuse_Final" , meaning that if yellow, blue or green is 0 and no other values are >0 then Current_Abuse_Final=0. This was done by recoding missing values for yellow, blue and green "current abuse" as "-1", then recoding zeros if "Yellow_Current_Abuse <1 and Green_Current_Abuse<1 and Blue_Current_Abuse<1"

Restructuring, grand mean centering the data across all time periods, group mean centering of the variables within each time period, and descriptive analysis of the data

was performed using *IBM SPSS Statistics for Windows*, (2013). The structural equation model was developed using Ωnyx, version 0.9-692 (Von Oertzen, Brandmaier, & Tsang, 2012), and the Open MX (Boker et al., 2012) model code generated by Ωnyx. Correlations were calculated among the stress, depression, anxiety, social support and tobacco use variables and the outcome variables presented in Chapter 4.

The indicator variables for the stress, depression, social support and tobacco use constructs were grand mean-centered and standardized. This allowed interpretation of the intercepts of the variables as the expected value of the outcome value when the predictor values are set to their means. For the path analysis, these same indicator variables were group mean-centered and then standardized so that the units of the regression coefficients would be the same throughout the model, and the various measures utilized in all of the manifest variables could be interpreted on a standard scale. When variables are mean-centered, the mean is subtracted from each individual data point, in order to provide a meaningful intercept. Grand mean-centering will allow between gestational time period comparisons to be made. But group mean-centering allowed the between group variation in means to be evaluated in the modeling.

For each model described below, covariance matrices are estimated with maximum likelihood estimation. To compare the fit of the models, likelihood ratios are used along with Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

Power Analysis

The reason for conducting a power analysis as a part of this study is to establish that given the available sample size there is enough power to actually detect a statistically significant difference that exists in the two models, and therefore reject the null hypotheses. Another way to explain statistical power is to say that the more power there is in the model, the less likely it is that there will be Type 2 error, of thinking there is no difference in the models being compared, when there actually is a difference. In other words, the power calculation explains how likely is it that we will obtain a p-value less than 0.05, given a particular effect size, our specific sample size and the assumption that alpha equals 0.05.

One of the advantages of a multilevel model technique such as SEM is that it accounts for the variance of error in the sample, thus requiring fewer subjects to produce a given level of power (MacCallum, Browne, & Sugawara, 1996). Measurement error that is inherent in the predictor variables could cause a single indicator model to produce imprecise results that can dilute the actual effect of the construct being measured. By creating latent constructs that are composed of multiple indicators, even only two, this random measurement error in the overall latent construct is reduced, thus improving the reliability of the model measurement, or power (Von Oertzen, Hertzog, Lindenberger, & Ghisletta, 2010).

The measurement model and the path model in SEM require distinct approaches to power analysis. The first analysis of power is actually for the confirmatory factor analysis. Bentler & Chou (1987) suggest that there should be at least 10 participants per free parameter. This is a very simplistic and not particularly accurate method of assuring

adequate power. However, since the lowest sample size in any of the seven groups is 128, and the constructs load to only two variables, reducing this CFA to a simple correlation, this sample size is more than sufficient.

In these correlations, the resulting r, is a summary statistic for significance and a representation of the effect size. The full SEM model provides us with effect sizes in the form of regression coefficients. Obviously, these effect sizes cannot be known *a priori*, however, once we have them, we can confirm that we had enough power to reject the null at a given level of statistical significance and sample size.

Estimating power for the full SEM, including the path model, which is a much more complicated model, demands an involved methodology for power analysis. Monte Carlo simulation can be used to determine power in these complex models (Muthén & Muthén, 2002). This technique generates data from a population of hypothesized parameters using thousands of simulated data samples to estimate the model parameters. These parameter values and their standard errors can then be averaged over these numerous samples, which ultimately allows for model power estimates for given sample sizes. Thus, Monte Carlo simulations were used to calculate power for this model. These simulations were run using an assumed alpha of 0.05. The sample size for the calculation of these curves was 125, because the smallest group in the restructured data contains 128 subjects.

The power analysis was run comparing two models, the null, and the alternate model. This alternate model states that there is a difference in regression weights across the different group time periods. R code developed by Kim (2012) was utilized in this

power analysis. In this case, after running the multiple simulations using the model, the number of simulations that resulted in a significant chi-square (difference) between the population or null model and the alternate model determined the power.

The Monte Carlo simulation evaluated the power needed to detect the smallest possible difference in model. Specifically, we wanted to determine whether the analysis could detect the difference in fit when the models were identical except for a single change in one path coefficient between two time points only (see Figure 3.2). The difference varies between zero and one, with zero meaning there is no difference between the two models. As the effect size increases, so does the statistical probability of detecting significant difference between two samples, or the sample and the general population.

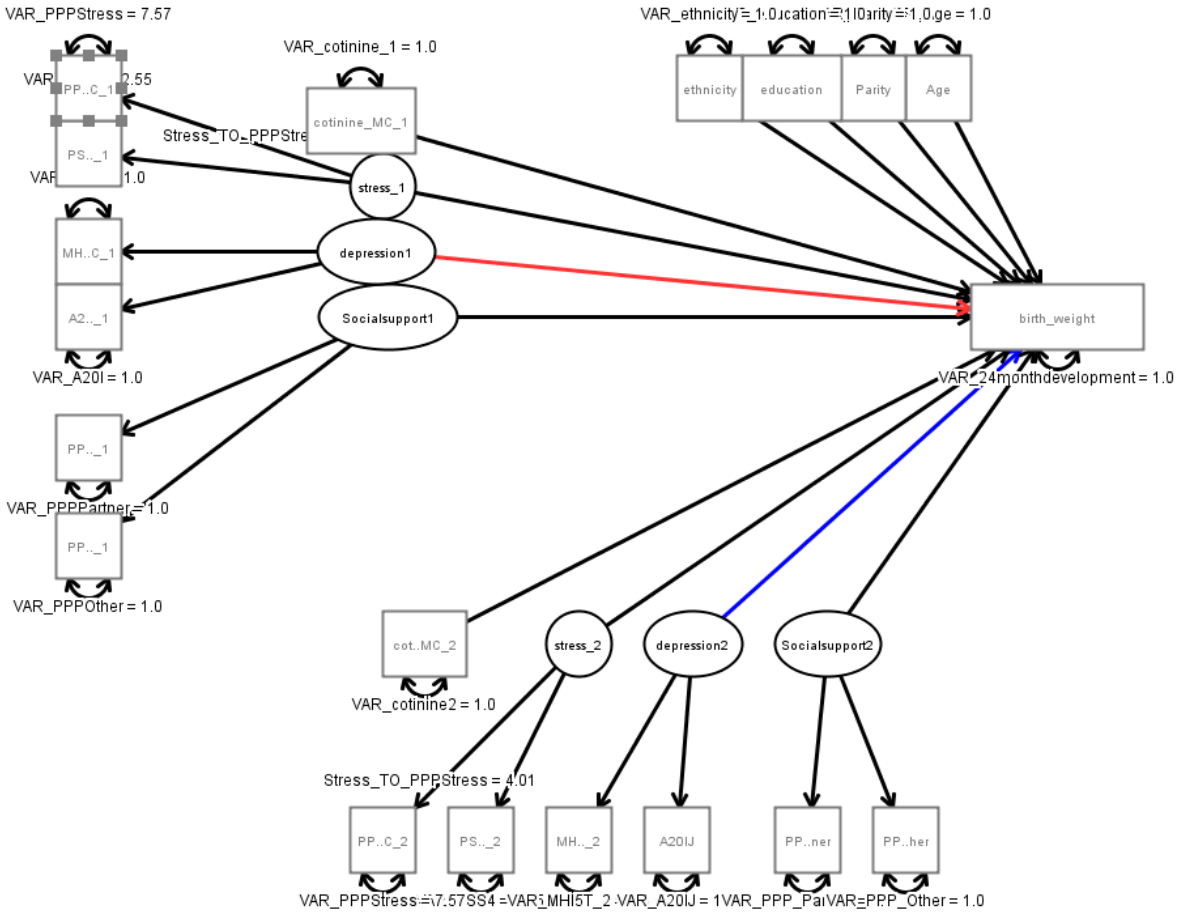

Figure 3.2 Parsed SEM model for calculation of power analysis with latent differences. The red line from depression 1 to birthweight and the blue line from depression 2 to birthweight are the only two different weights in the model tested by Monte Carlo simulation. All other regression paths from other latent variables and manifest variable to birthweight are the same.

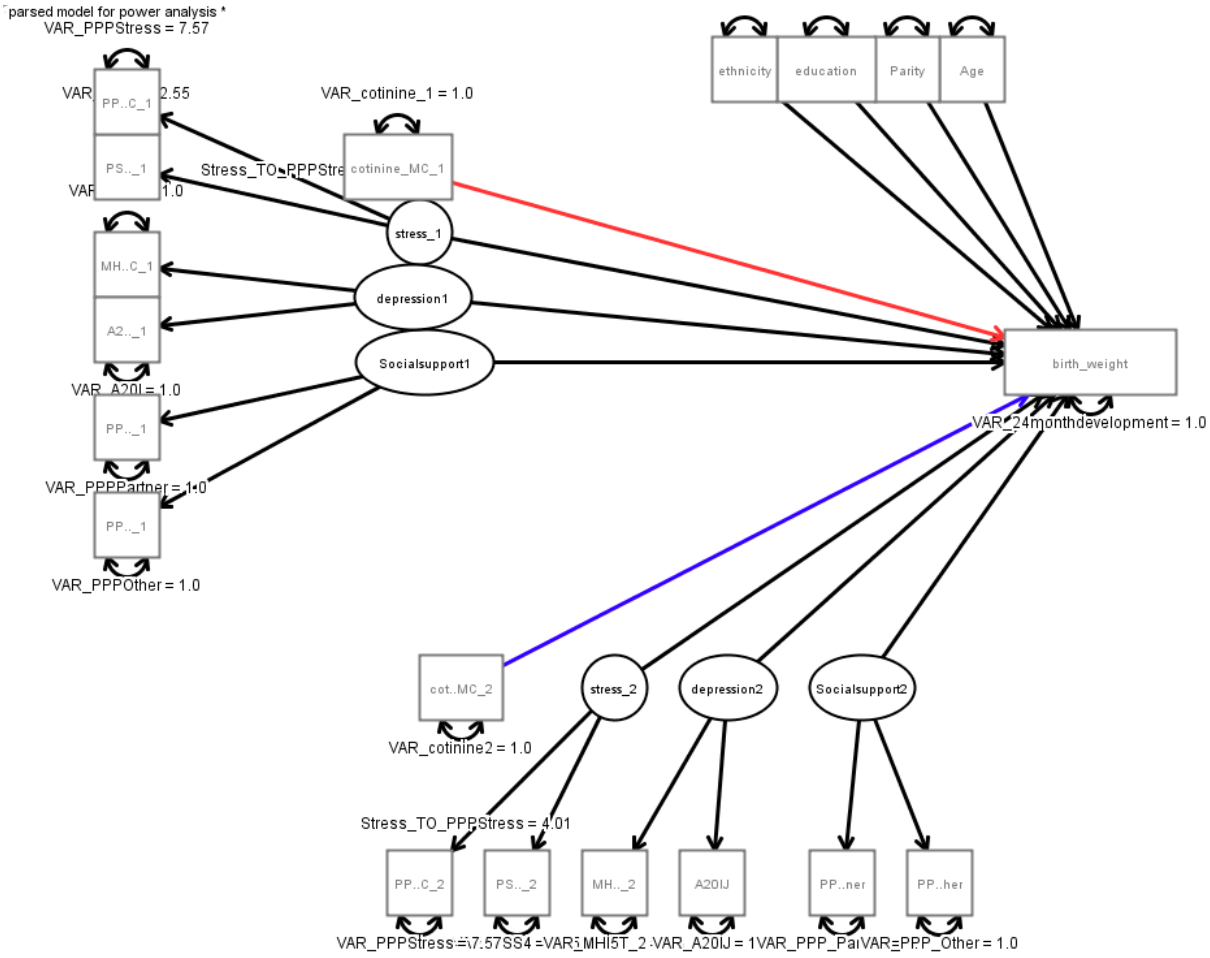

Figure 3.3 Parsed SEM model for calculation of power analysis with manifest differences. The red line from cotinine 1 to birthweight and the blue line from cotinine 2 to birthweight are the only two different weights in the model tested by Monte Carlo simulation. All other regression paths from latent variables to birthweight are the same.

Two power curves were generated. Both are represented in Figure 3.4 as the power by effect size (effect size on the x axis and power on the y axis) of a difference in the manifest variable regressed on the dependent variable, or the difference in a latent variable regressed on the dependent variable.

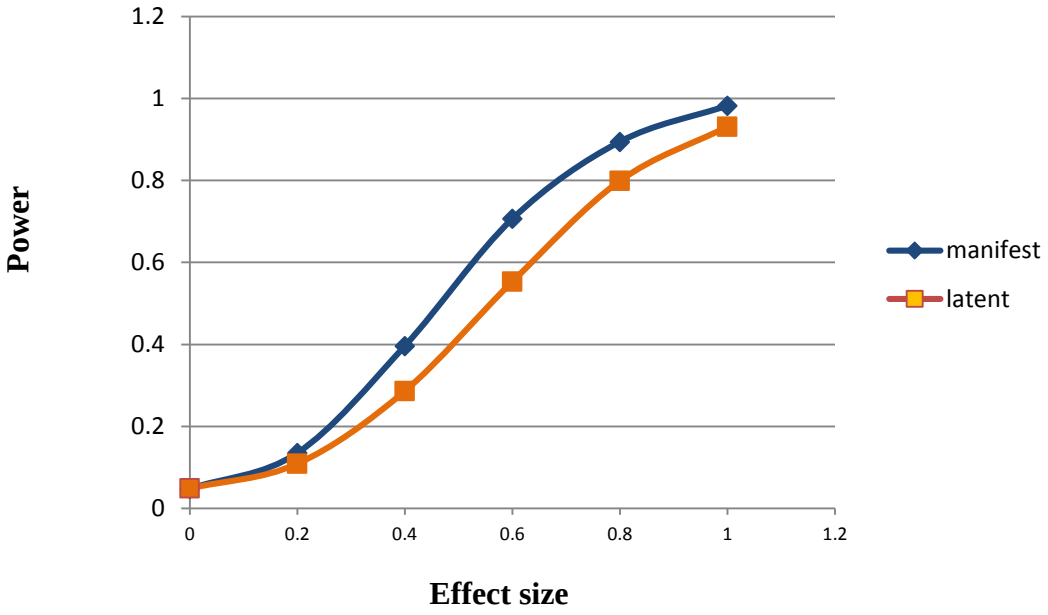

Figure 3.4 Power versus Effect size. Power to detect a difference in one single regression weight of manifest variable (blue triangles) and latent variables (orange squares), when α=0.05 and n=125. The solid lines represent the estimated power for this model.

Missing Data

The analysis design works with planned missingness. Each participant is measured at two of the seven gestational time periods, the rest is considered and expected to be missing. In this way, full information of the data can be explicated using Full Information Maximum Likelihood techniques within the modelling process (Olinsky, 1999).

Evaluation of Specific Aim #2

Specific aim 2 (see Table 3.4) seeks a more complete understanding of the associations in the data to both illuminate understandings about the population differences in abused versus not currently abused women and also to guide future work. Linearity of the relationships over time of amount of tobacco use, stress, depression, and

social support was done using SPSS statistical package (*IBM SPSS Statistics for Windows*, 2013) to calculate the grand means across groups, then grand mean center the variables within each group, to obtain individual group means based upon the grand mean, which were then plotted. Assessing linearity through the creation of grand mean plots for each of the latent variables and cotinine, offers insight into whether latent growth curve modeling might be applied in future studies, and also helps to evaluate overall trends in data. If these plots of the means are curvilinear or quadratic, this suggests that future evaluation of this data could be accomplished using latent growth curve modeling. When these plots are calculated on the split groups (abused versus not currently abused), it may provide insight into the differences in latent variable impact in these separate populations.

Evaluation of Specific Aims 1 & 3: Model Testing Strategy

The analysis for specific aims 1 and 3 (see Table 3.4) was conducted using the tenets of SEM.

SEM is a useful statistical technique that combines both factor and path analysis, and accounts for measurement error in the modeling process. SEM aims to estimate the magnitude and significance of postulated causal connections between sets of variables. It was originally designed as a way to test theoretical constructs that attempt to explain phenomena. Most SEM methods are similar to regression because they are both general linear models. Basic SEM allows one to perform simple statistical analyses such as t-tests or ANOVAs . It is also possible to utilize multi-level models and latent growth curve modeling within the context of SEM, allowing the examination of continuous

development over time. It is particularly useful in the case of this dataset because the modeling technique can handle non-normal data, reduce type 1 measurement error, and also handle missing values. When the data is restructured into seven time periods, each subject has missing values for at least four time points, since data was only collected three times (twice during pregnancy).

Model testing was conducted in three phases. The first step is to perform confirmatory factor to determine how well the chosen manifest variables represented the latent constructs of stress, depression, anxiety, and social support at each time period. Because there are only two manifest variables in each construct, simple correlations provide the optimal fit for these three latent constructs.

The second phase of testing consists of constructing a model to represent the impact of the latent variables and tobacco use (represented by cotinine) at the seven gestational periods on gestational age (EGA) at birth. Direct paths are added between the latent variables and continine for each time period and the dependent variable, either gestational length or birthweight.

The third phase of this procedure involves establishing the best fit for the multilevel regression model. For the first hypothesis, a null model that states there are differences in regression weights across groups is compared to the full interaction model at each time period as described in Figure 3.5 for birthweight and in Figure 3.6 for gestational length. For the second hypothesis, that there is a difference between the pattern of regression weights between the abused women and those who are not currently abused, the models depicted in Figure 3.5 and 3.6 are loaded with data from these two groups, and then compared.

Covariance matrices from these models were estimated with maximum likelihood estimation using OpenMx (Boker et al., 2012) in R (R Development Core Team, 2013). Fit evaluation was attempted by both the absolute measure of Root Mean Square Error of Approximation RMSEA, and by using both the Minus Two Log Likelihood (-2LL) and Akaike Information Criteria (AIC) as measures of comparative fit. The differences between each model's AIC and the more constrained model is used to determine chi-square changes for significance. Regression paths are also obtained in each model.

To address the first specific aim, confirmatory factor analysis was performed to determine how well the chosen manifest variables represented the latent constructs of stress, depression, anxiety, and social support, loading the factors at all time points into one model. Because there are only two manifest variables in each construct, simple correlations provide the optimal fit for these four latent constructs.

Table 3.4
Analytic Methods by Study Aim

Specific Aims	**Analytic Methods**
1. To identify the latent variables in the BabyBEEP dataset relating to stress, depression, anxiety and social support.	**Confirmatory factor analysis** using **structural equation modeling** of: a. The latent construct "stress" loadings on the indicator variables perceived stress/anxiety and appraisal of stress. b. The latent construct of "Social Support" loadings onto the indicator variables of PPP- partner support, PPP- other person support. c. The latent construct "Depression" loadings onto the indicator variables of MHI-5, and sum of A2OI&J from the PPP self-esteem scale. This is accomplished through checking the correlations between the two manifest variables in each latent construct.
2. To determine the linearity of the relationship among tobacco use and the latent constructs of stress, depression, and social support over time.	For each of the latent constructs and cotinine data: **Plot mean curves** using a 2-way plot of grand centered means by time.
3. Determine the differences in patterns of stress, depression, tobacco use and social support impact across time on gestational length and birthweight in pregnancies exposed to abuse compared to those not exposed to abuse: a. Determine the association of tobacco use and the latent variables (social support, stress, and depression) at different gestational ages. b. Determine the impact of the latent variables on gestational length and birthweight after controlling for tobacco use during pregnancy.	**Structural equation modeling** of **:** a. Evaluate the covariance between these variables and gestational time period by creating A multilevel model (one for each time period) to determine and compare the significant interactions between tobacco use and social support, stress, and depression, using the latent variables that were confirmed by cfa in aim # 1 b. Structural equation modeling to evaluate the full research theoretical model across 7 stages of gestation. c. Compare the population model of nonabused women to the model with abused women

Structural equation models such as the one found in Figures 3.2, 3.3, 3.5 and 3.6 can be understood as follows: The straight arrows from the latent constructs to the

measured or manifest variables indicate that the latent constructs predict the measured variables. The curved two-headed arrow attached to each manifest variable represents the random effects or residuals which constitute the unknown error in the variable model. The straight arrows from the latent constructs to the outcome variable represent the path weight or beta values.

There are two hypotheses to be considered. The first question asked is whether it fits the data that the impact of the latent constructs, stress, depression and social support, along with the manifest variable of tobacco use, varies significantly across the gestational time periods in regard to outcome. This will be evaluated within the single model. We will also to evaluate whether the variance is different in abused women than in a group of not currently abused women.

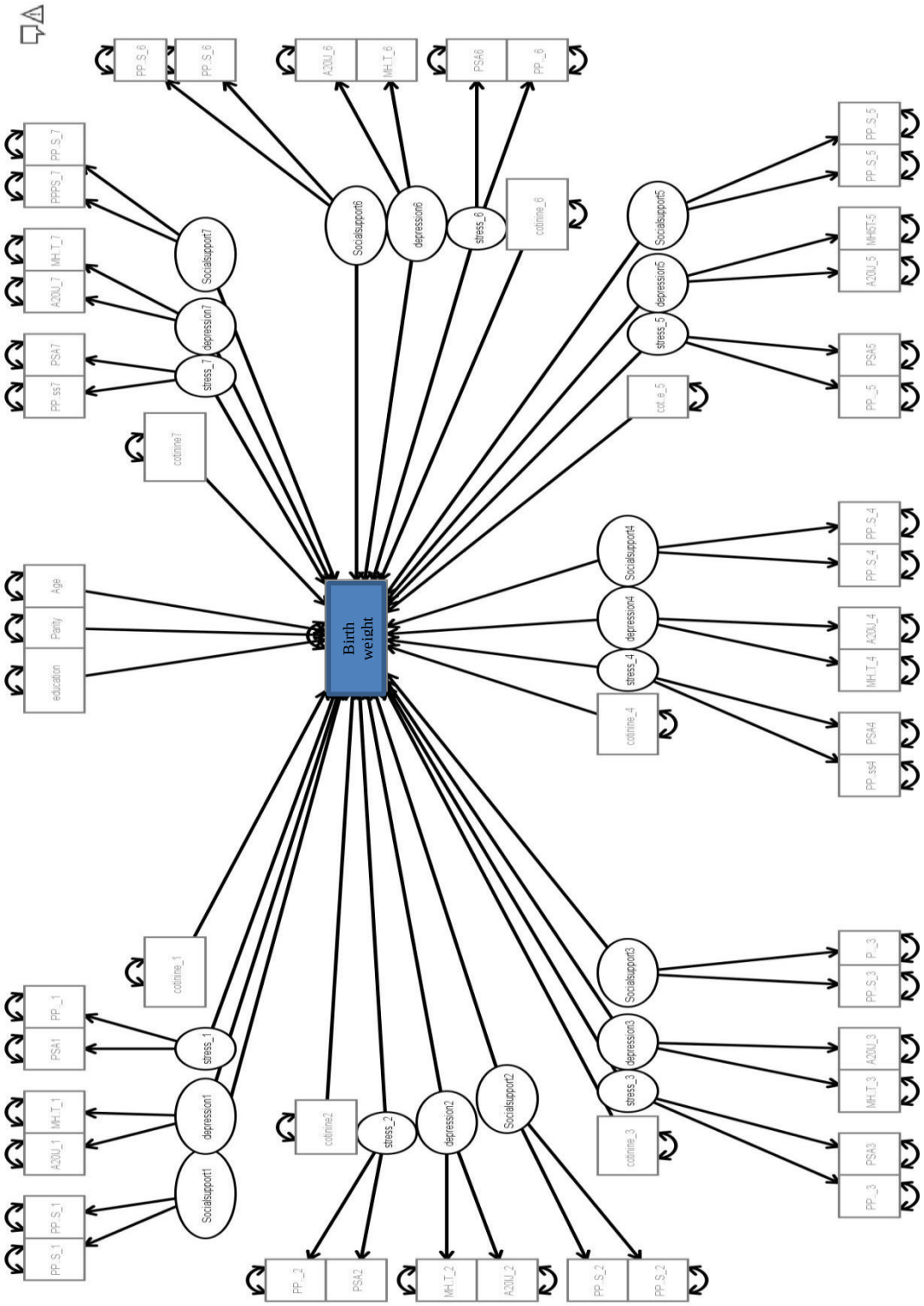

Figure 3.5 The full structural equation model for birthweight.

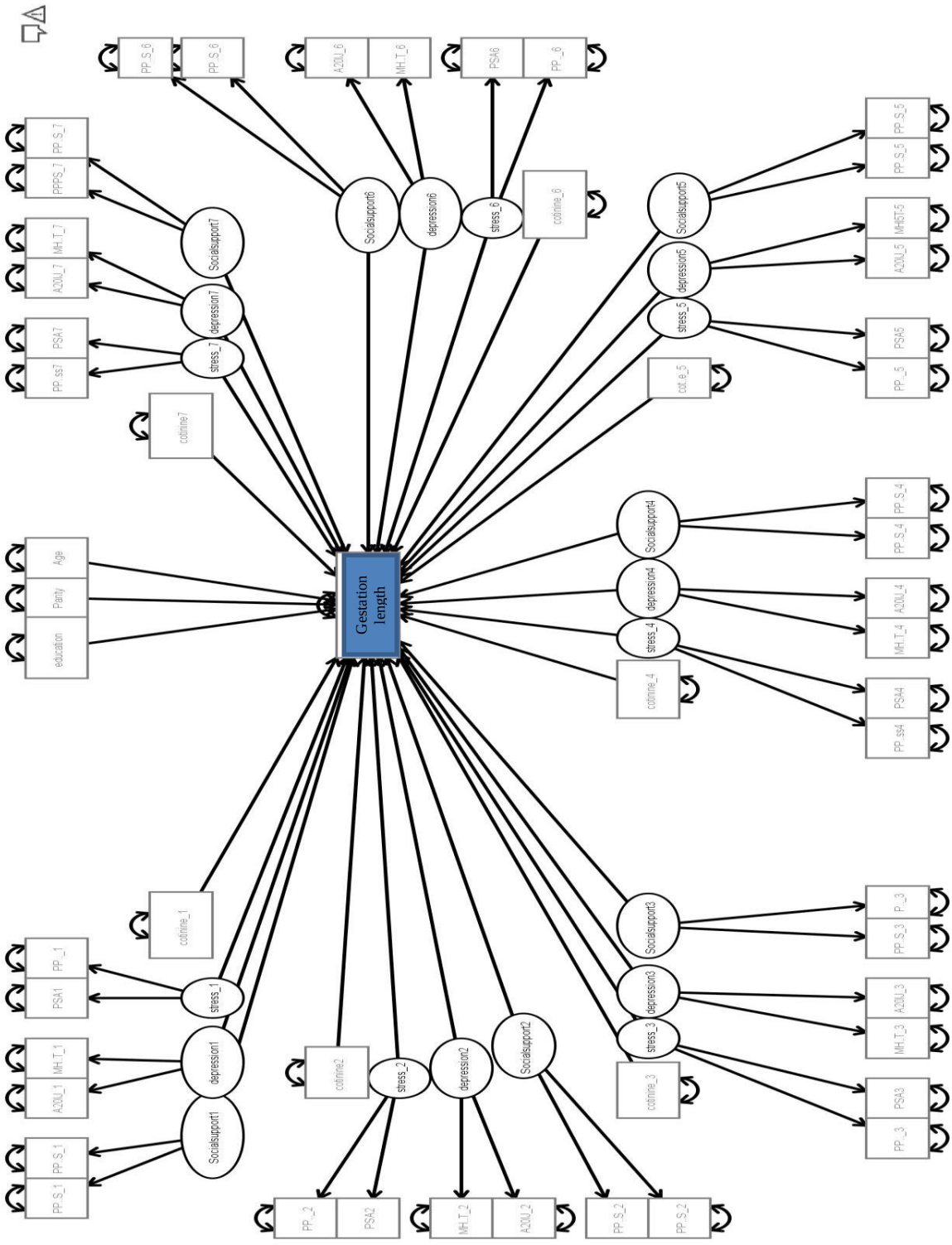

Figure 3.6 The full structural equation model for length of pregnancy

Model Identification

A model is just-identified when the number of data points is equal to the number of parameters to be estimated. The number of data points in the model is the number of variances (and covariances if any were included in the model, which they were not for this study), and is given by $p(p+1)/2$, where p equals the number of observed variables. The number of parameters to be estimated is the number of fixed effects (beta values), and random effects (error) specified in the model. The number of data points is 52(52+1)/2=1378, and the model requires 125 parameters to be estimated (73 beta weights and 52 random effects). Thus, the model under consideration is over-identified. There will be 1378-125=1253 degrees of freedom (*df*s) when the fit of the data to the model is tested.

The evaluation of BabyBEEP data fit to this model will be done using SEM conducted using OpenMx (Boker et al., 2012) and R (R Development Core Team, 2013) statistical packages to evaluate the third specific aim. Covariance matrices will be estimated with maximum likelihood estimation using robust standard errors to test the multiple hypothesized direct and indirect relationships between variables that are mapped in Figure 3.1 and described in the specific aims. Robust standard errors will be used because the nature of pregnancy related data, especially length of gestation and birthweight, is non-parametric. The third phase of this procedure involves establishing the best fit for the full multilevel SEM regression model. All parameters are estimated simultaneously, controlling for all other effects in the model. If the linearity in aim #2 indicates that aim #3 should be evaluated, multiple measures of fit will be assessed,

including Chi-square, RMSEA, and Akaike Information Criterion. If aim #4 is the appropriate choice for analysis then extensive bootstrapping will be done to determine if the model at one time point is larger than the others and/or base confidence intervals assessed to determine the restrictive model that has best model fit with the data.

Limitations

There are several limitations that affect our ability to test the theoretical model of Adaptive Reproduction using the BabyBEEP data. Aside from the inclusion criteria (low-income rural women), the dataset does not contain any community level data, leaving the full theoretical model testing to future prospective work. Not all the constructs posited as important in the prenatal stress process literature have validated composite measures included in the BabyBEEP dataset. The abuse variable, without having a validated measure of severity of abuse, and only dichotomized screening questions, could not be included as a covariate in this model. Future work should attempt to model abuse severity as a continuously measured environmental stressor. For this study, by putting these two sets of women, "currently-abused", and "not currently abused", into two identical but separate models, a comparison could be made between the two groups of women.

For the purposes of this study I chose to compare models of "not currently abused" with a model of "currently abused" women. However, interpretation of this model assumes that in reporting abuse or lack of abuse, women were being truthful. Although a positive answer fairly certainly indicates the woman is being or has been abused, a negative answer does not insure that she will not disclose past abuse at a future screening date. Studies have shown that repeated screening over time identifies more

women with risk exposures (Kiely, Gantz, El-Khorazaty, & El-Mohandes, 2013). These women are not just reporting ongoing new incidents, but with repeated screening will admit to lifetime abuse or abuse in the last year that was not previously disclosed. In spite of including any person in the "currently abused" category if they reported abuse at any time point in the original study, there is still the possibility that some of the women who are evaluated in the "not currently abused" group simply did not yet disclose the abuse.

By choosing to evaluate only currently abused women, the more inclusive category of "ever abused" women, identified by the first question in the AAS, are excluded from the analysis. This presents a possibly significant limitation to this work, because of the potential confounding effect of post-traumatic stress on both the woman's overall mental health and cell-signaling patterns. Future work should evaluate the impact of past abuse on risk exposures, cell signaling during pregnancy and birth outcomes.

Another limitation is that there is no measure of current emotional or psychological abuse in this dataset. It is possible that emotional or psychological abuse has an even greater impact on the pregnancy outcome than physical or sexual abuse.

The dataset does not contain information about whether the women who were depressed were medicated for their depression or not. Use of antidepressants may change the outcomes of interest unforeseen ways. Future research should account for this covariate when evaluating depressed pregnant women.

There are also constraints that relate to enrollment issues that are inherent in many studies that utilize pregnant women. For instance, because women were enrolled at

different gestational ages up to 24 weeks EGA, the model may not appropriately reflect rates of early pregnancy loss in this population, which may misrepresent gestational length as a measure of poor outcome. The mean EGA at enrollment was 13.5 weeks EGA, suggesting that early pregnancy loss due to adaptive reproductive causes cannot be evaluated using this dataset. The incidence of pregnancy loss prior to viability in the BabyBEEP study was only 1.5%. These post-enrollment losses could arguably be more related to environmental factors than fetal anomalies, and are included in the analysis of gestational length.

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Chapter 4: Results

Introduction

The analysis reported in this dissertation was performed to test the fit of the theoretical model of adaptive reproduction to the data from the BabyBEEP study (R01NR05313). Data analysis was accomplished in several stages. Descriptive analyses of the demographic variables for BabyBEEP were described previously in Chapter 3 (see Table 4.1). Further descriptive analysis was performed on observed variables of interest and is described here. This was followed by establishing the measurement model through confirmatory factor analysis, evaluation of the structural model through path analysis and assessment of model fit using Structural Equation Modeling (SEM). Preliminary data preparation was described in Chapter 3. The results of data analysis are presented in this chapter. The findings are discussed in four sections: 1) Descriptive analysis of the variables of interest in the BabyBEEP dataset; 2) Specific Aim 1; 3) Specific Aim 2; and 4) Specific Aim 3.

Descriptive Analysis

The demographic analysis of the total sample from the BabyBEEP study is presented first (Table 4.1). For the purposes of this analysis, the original sample was restructured by gestational age at time of each interview, as described in Chapter 3 so that each interview point provides cross-sectional data belonging to one of seven particular gestational age groups, from the fourth through the end of thirty-sixth gestational week (see Table 4.2). This yielded a total of 1305 measurements from the original 695 women who participated in the study. Birth outcome data was available for 632 of those women

and 9 of those were removed from the data set as outliers because they delivered prior to 21 weeks. This left 623 women, in the restructured data set, yielding 1246 data points. There were only 13 women for whom data was collected between the thirty-seventh week of gestation until delivery. Given this small size of this group, those particular 13 measurements were excluded from the modeling.

Table 4.1

BabyBEEP Participant Demographic Characteristics

	BabyBEEP	Current Study
Measure	Total N=695	N=623
Age ,Mean (SD)	23.7(4.7)	23.1(4.6)
Parity, Mean (SD)	1 (1.14)	1(1.15)
Years of Education, Mean (SD)	11 (1.7)	11(1.7)
Abused, n (%)	227(32.7)	213(34.2)
Ethnicity, n(%)		
Caucasian	630 (90.6)	568(91)
African American		
Latina	24 (3.5)	20(3.2)
Asian American		
Native American	12(1.7)	9(1.4)
Other	2(0.3)	2(.3)
	10(1.4)	10(1.6)
	17(2.4)	14(2.2)
Tobacco Use Prior to Pregnancy per day, n(%)		
10 or less	104 (15)	
11-20	320(46)	
21-30	192(28)	
31 or more	79(11)	

Table 4.2
Gestation Age Group Composition

Gestational Age	Group Number	n
4-9 weeks	1	100
10-13 weeks	2	219
14-18 weeks	3	175
19-23 weeks	4	121
24-28 weeks	5	161
29-31 weeks	6	296
32-37 weeks	7	143
Total		1215

Demographics

A summary of characteristics for demographic variables is presented in Table 4.1. The mean age of the 695 participants recruited for the BabyBEEP study was 23.7 years (SD=4.7). Although the average amount of education was 11 years (SD=1.7), the majority had either a high school diploma or GED (63%). Most participants were living with a partner (70%). The mean gestational age at enrollment was 13.5 weeks. Eighty-five percent of the women smoked at least 11 cigarettes a day prior to pregnancy and all women were smoking upon enrollment in the study. All of these women were low-income as measured by their eligibility for WIC; they were recruited from WIC clinics.

The majority were Caucasian (91%), which is consistent with the population demographics in the geographical study area. This ethnic homogeneity led to the decision to exclude race from the model, in spite of the significant disparities that exist in gestational length outcomes that affect African American women in particular.

The demographic composition of each group is presented in Table 4.3. One-way ANOVAs were performed on the seven groups included in the full analysis in order to

determine if there were group differences in the means of demographic variables. There were not any significant differences found.

Table 4.3

Demographic Comparisons between Groups

	Group 1 N=100	Group 2 N=219	Group 3 N=175	Group 4 N=121	Group 5 N=161	Group 6 N=296	Group 7 N=143
Variable	4-9 wks	10-13 wks	14-18wks	19-23wks	24-28 wks	29-31 wks	32-37 wks
Age, mean, SD	23.37(4.4)	22.69(4.1)	23.64(5.31)	3.02(4.51)	22.83(4.4)	22.91(4.6)	23.89(4.78)
Education	11.18(1.5)	11.43(1.8)	11.5(1.67)	11.19(1.69)	11.23(1.57)	11.35(1.67)	11.41(1.8)
Married%, (N)	73.4(94)	68.6(162)	67.7(132)	70.3(90)	72.0(116)	70.7(210)	70.1(103)
Caucasian	89.8(94)	90.3(213	91.3(178)	90.6(116)	93.2(150)	90.9(270)	91.8(135)
Nulliparous	43.8(56)	48.7(115)	44.6(87)	43.8(56)	44.1(71)	44.4(132)	41.5(61)

Note. There were no statistically significant differences in the means of the above variables. All groups had non-significant F values in a one-way ANOVA.

Analysis of Variables of Interest

Overall mean scores for the manifest variables in this model are presented in Table 4.4. The mean gestational length for this sample of 38.7 weeks (or 38 weeks 5/7 days) falls into the category from 37 0/7 weeks to 38 6/7 weeks gestation that is currently referred to as early term. Early term births are associated with increased neonatal morbidity (Fleischman, Oinuma, & Clark, 2010). The mean scores for the group of women who were scored positive for intimate partner violence (IPV) is presented in Table 4.5 and the means for their counterparts, the IPV negative women are presented in Table 4.6

Mean birthweight in this total sample was 3178 grams. This included births at any gestation after 21 weeks. In comparison, the mean birthweight for babies born

between 37 and 41 weeks across the United States during this study period was 3389 grams (Donahue, Kleinman, Gillman, & Oken, 2010).

The original study was a tobacco cessation study in which Cotinine means dropped as the pregnancies progressed. This is demonstrated by general trend of decreasing means with increasing group number.

The stress construct, composed of the perceived life stressors measured by the PPP Stress subscale (Curry, Burton, & Fields, 1998) and perceived stress and anxiety measured as the PSA, combining the Cohen's PSS (Cohen, Kamarck, & Mermelstein, 1983) , the worry and emotionality questions from the MHI-5 (Rumpf, Meyer, Hapke, & John, 2001) and the fear question from the AAS(McFarlane & Parker, 1994). There was less than a ten percent variation in scores on the PPP Stress subscale measuring perceived life stressors. The PSA demonstrated a very small across group variance, at four percent.

Depression was constructed from the MHI-5 reverse calculated score and the answers to questions on the PPP self-esteem subscale about having a sense of worthlessness (A20IJ). There was a total variation of 18 percent across means for the MHI-5 across groups. The nadir of MHI-5 means was at Group 5 and 6 with the highest mean at Group 4. The means on the sense of worthlessness questions were steady across groups at just over 4 on a scale of eight.

The concept of social support was evaluated based on partner support using the PPP Partner Support subscale, and on other support measured by the PPP Other Support subscale. There was a 12 percent drop in means over time for Partner Support. These

means were lower than the means for Other Support, which also had only a 5 percent variation across groups.

Table 4.4

Means, Standard Deviations and Skewness for Restructured BabyBEEP Dataset

				Skewness		
	N	Mean	Standard Deviation	Skewness Statistic	Standard. Error	Skewness coefficient
Gestational Length	623	38.7	2.2	-2.634	.098	-26.8776
Birthweight	610	3178	546	-.956	.099	-9.65657
Parity	623	1	1.15	1.366	.098	13.93878
Age	623	23.12	4.60	1.273	.098	12.9898
Education	623	11.34	1.68	.232	.098	2.367347
PPP_Stress 1	100	21.53	4.80	.260	.241	1.078838
PPP_Stress 2	219	21.87	5.32	.420	.164	2.560976
PPP_Stress 3	175	21.15	5.01	.481	.184	2.61413
PPP_Stress 4	121	22.50	4.69	.358	.220	1.627273
PPP_Stress 5	161	20.43	4.83	1.011	.191	5.293194
PPP_Stress 6	296	19.38	4.86	.737	.142	5.190141
PPP_Stress 7	143	20.91	5.55	.775	.203	3.817734
PSA 1	100	18.01	3.34	-.440	.241	-1.82573
PSA 2	219	17.69	3.20	-.175	.164	-1.06707
PSA 3	175	18.19	3.28	-.101	.184	-0.54891
PSA 4	121	18.42	3.36	-.550	.220	-2.5
PSA 5	161	17.90	3.07	.207	.191	1.08377
PSA 6	296	17.69	3.16	.466	.142	3.28169
PSA 7	143	17.89	3.41	.301	.203	1.482759
MHI5 (Reversed) 1	95	42.27	19.42	.251	.247	1.016194
MHI5 (Reversed) 2	207	39.71	17.58	.226	.169	1.337278
MHI5 (Reversed) 3	169	39.50	18.74	.362	.187	1.935829
MHI5 (Reversed) 4	117	44.10	18.97	.269	.224	1.200893
MHI5 (Reversed) 5	159	34.84	18.99	.476	.192	2.479167
MHI5 (Reversed) 6	296	34.35	18.36	.862	.142	6.070423
MHI5 (Reversed) 7	143	41.17	20.52	.624	.203	3.073892
A20IJ 1	100	4.58	1.65	.069	.241	0.286307
A20IJ 2	219	4.43	1.56	.066	.164	0.402439
A20IJ 3	175	4.43	1.55	.199	.184	1.081522

	N	Mean	Standard Deviation	Skewness Statistic	Skewness Standard. Error	Skewness coefficient
A20IJ 4	121	4.70	1.49	.035	.220	0.159091
A20IJ 5	161	4.40	1.38	.025	.191	0.13089
A20IJ6	295	4.21	1.42	.001	.142	0.007042
A20IJ7	143	4.29	1.43	.278	.203	1.369458
PPP Other Support 1	100	47.14	15.93	-1.380	.241	-5.72614
PPP Other Support 2	219	53.90	11.35	-2.088	.164	-12.7317
PPP Other Support 3	175	53.00	12.24	-1.656	.184	-9
PPP Other Support 4	121	50.93	13.43	-1.308	.220	-5.94545
PPP Other Support 5	161	51.32	13.00	-1.518	.191	-7.94764
PPP Other Support 6	296	53.03	12.09	-1.653	.142	-11.6408
PPP Other Support 7	143	50.98	15.23	-1.698	.203	-8.36453
PPP Partner Support 1	100	48.12	17.28	-1.359	.241	-5.639
PPP Partner Support 2	219	45.98	19.99	-1.328	.164	-8.09756
PPP Partner Support 3	175	44.80	21.75	-1.229	.184	-6.67935
PPP Partner Support 4	121	44.99	20.99	-1.239	.220	-5.63182
PPP Partner Support 5	161	47.88	19.11	-1.522	.191	-7.96859
PPP Partner Support 6	296	45.44	21.86	-1.196	.142	-8.42254
PPP Partner Support 7	143	42.39	22.85	-.953	.203	-4.69458
Cotinine 1	82	144.02	111.37	1.833	.266	6.890977
Cotinine 2	193	132.12	100.81	1.397	.175	7.982857
Cotinine 3	264	132.22	100.89	1.415	.150	9.433333
Cotinine 4	311	129.94	96.99	.980	.138	7.101449
Cotinine 5	298	134.07	96.92	.737	.141	5.22695
Cotinine 6	261	117.10	90.86	1.004	.151	6.649007
Cotinine 7	281	116.82	95.71	1.132	.145	7.806897

Note. From BB. H1.FINAL.1_9_14.sav

Table 4.5
Means, Standard Deviations and Skewness for IPV Positive Women Only in the Restructured BabyBEEP Dataset

	N	Mean	Std. Deviation	Skewness		
				Statistic	Std. Error	Skewness Coefficient
Gestational Length	213	38.49	2.31	-2.714	.167	-16.2864
Birthweight	209	3157.35	548.51	-1.056	.168	-6.27957
Parity	213	0.98	1.12	1.169	.167	7.010928
Age	213	22.45	4.30	1.279	.167	7.676472
Education	213	11.04	1.72	.395	.167	2.368077
Cotinine_O_G1	24	111.39	75.90	.775	.472	1.640507
Cotinine_O_G2	62	141.06	100.71	.512	.304	1.684399
Cotinine_O_G3	87	120.49	106.09	2.718	.258	10.52612
Cotinine_O_G4	98	131.47	102.37	1.545	.244	6.338213
Cotinine_O_G5	97	138.80	100.81	.925	.245	3.776139
Cotinine_O_G6	80	122.41	93.66	1.104	.269	4.106389
Cotinine_O_G7	94	116.16	86.64	.538	.249	2.163233
PPP_Stress_G1	33	23.82	5.38	.089	.409	0.217122
PPP_Stress_G2	71	23.55	5.55	.282	.285	0.989165
PPP_Stress_G3	61	22.34	4.73	.601	.306	1.963569
PPP_Stress_G4	46	24.30	4.94	.525	.350	1.500546
PPP_Stress_G5	57	22.07	5.63	1.161	.316	3.669059
PPP_Stress_G6	97	21.11	4.91	.927	.245	3.782947
PPP_Stress_G7	54	23.22	5.77	.742	.325	2.286535
PSA_G1_O	33	19.09	2.95	-.149	.409	-0.36431
PSA_G2_O	71	17.80	3.56	-.382	.285	-1.34255
PSA_G3_O	61	18.70	3.60	-.493	.306	-1.60904
PSA_G4_O	46	19.13	3.32	-.229	.350	-0.65526
PSA_G5_O	57	18.23	3.38	.164	.316	0.518447
PSA_G6_O	97	18.42	3.36	.839	.245	3.425948
PSA_G7_O	54	18.89	3.92	.137	.325	0.422081
MHI5R 1	31	47.48	21.08	-.048	.421	-0.11415
MHI5R 2	67	45.79	16.42	-.404	.293	-1.37819
MHI5R 3	58	44.34	18.14	.234	.314	0.745982
MHI5R 4	46	50.70	18.76	-.043	.350	-0.12269
MHI5R 5	56	41.00	20.29	.405	.319	1.270859
MHI5R 6	97	37.32	18.12	.430	.245	1.754688
MHI5R 7	54	50.15	21.12	.506	.325	1.559662
A20IJ 1	33	4.64	1.85	.132	.409	0.323362
A20IJ 2	71	4.80	1.55	-.154	.285	-0.54015
A20IJ 3	61	4.92	1.64	.136	.306	0.443587
A20IJ 4	46	5.02	1.61	-.103	.350	-0.29496
A20IJ 5	57	5.00	1.15	-.146	.316	-0.46217
A20IJ 6	96	4.58	1.37	-.318	.246	-1.29069

	N	Mean	Std. Deviation	Skewness		
				Statistic	Std. Error	Skewness Coefficient
A20IJ 7	54	4.70	1.41	.133	.325	0.409147
PPP_O_Support_G1	33	45.48	18.20	-1.260	.409	-3.08366
PPP_O_Support_G2	71	51.73	14.08	-1.927	.285	-6.76707
PPP_O_Support_G3	61	47.90	14.91	-.996	.306	-3.25322
PPP_O_Support_G4	46	48.17	14.11	-.974	.350	-2.7809
PPP_O_Support_G5	57	49.30	14.79	-1.370	.316	-4.33082
PPP_O_Support_G6	97	51.05	13.54	-1.337	.245	-5.45569
PPP_O_Support_G7	54	48.07	16.67	-1.115	.325	-3.43457
PPP_P_Support_G1	33	43.18	17.80	-.511	.409	-1.25058
PPP_P_Support_G2	71	40.10	22.64	-.797	.285	-2.80014
PPP_P_Support_G3	61	41.48	23.27	-.941	.306	-3.07173
PPP_P_Support_G4	46	35.80	23.96	-.513	.350	-1.4646
PPP_P_Support_G5	57	46.82	19.54	-1.446	.316	-4.56982
PPP_P_Support_G6	97	41.92	23.54	-.863	.245	-3.52458
PPP_P_Support_G7	54	37.44	23.78	-.518	.325	-1.59668

Table 4.6
Means, Standard Deviations and Skewness for IPV Negative Women Only in the Restructured BabyBEEP Dataset

				Skewness		
	N	Mean	Std. Deviation	Statistic	Std. Error	Skewness Coefficient
Gestational Length	410	38.77	2.16	-2.593	.121	-21.5141
Birthweight	401	3189.47	545.34	-0.907	.122	-7.44354
Parity	410	0.93	1.17	1.462	.121	12.12841
Age	410	23.47	4.72	1.263	.121	10.47848
Education	410	11.50	1.65	.174	.121	1.442416
Cotinine_O_G1	58	157.53	121.11	1.767	.314	5.631994
Cotinine_O_G2	131	127.89	100.97	1.831	.212	8.653908
Cotinine_O_G3	177	137.99	98.03	0.681	.183	3.730069
Cotinine_O_G4	213	129.24	94.66	0.659	.167	3.951803
Cotinine_O_G5	201	131.80	95.17	.630	.172	3.673332
Cotinine_O_G6	181	114.75	89.76	0.960	.181	5.317682
Cotinine_O_G7	187	117.17	100.20	1.317	.178	7.408877
PPP_Stress_G1	67	20.40	4.08	-.130	.293	-0.44554
PPP_Stress_G2	148	21.07	5.04	.450	.199	2.256077
PPP_Stress_G3	114	20.52	5.06	.514	.226	2.268984
PPP_Stress_G4	75	21.40	4.19	-.027	.277	-0.09847
PPP_Stress_G5	104	19.54	4.10	0.379	.237	1.59931
PPP_Stress_G6	199	18.54	4.62	.661	.172	3.836746
PPP_Stress_G7	89	19.52	4.94	.738	.255	2.889427
PSA_G1_O	67	17.49	3.42	-.464	.293	-1.58481
PSA_G2_O	148	17.65	3.04	-.037	.199	-0.18542
PSA_G3_O	114	17.93	3.08	.126	.226	0.556018
PSA_G4_O	75	18.00	3.35	-.781	.277	-2.81618
PSA_G5_O	104	17.72	2.90	.181	.237	0.764272
PSA_G6_O	199	17.34	3.01	.157	.172	0.910205
PSA_G7_O	89	17.29	2.92	.065	.255	0.256119
MHI5R 1	64	39.75	18.21	.348	.299	1.163063
MHI5R 2	140	36.80	17.43	.547	.205	2.671028
MHI5R 3	111	36.97	18.63	.474	.229	2.065213
MHI5R 4	71	39.83	17.97	.482	.285	1.691687
MHI5R 5	103	31.50	17.47	.404	.238	1.697002
MHI5R 6	199	32.90	18.36	1.098	.172	6.368296
MHI5R 7	89	35.73	18.21	.630	.255	2.467826
A20IJ 1	78	5.31	1.58	.000	.272	-0.00088
A20IJ 2	137	5.50	1.52	-.001	.207	-0.00343
A20IJ 3	122	5.66	1.69	-.262	.219	-1.19615

	N	Mean	Std. Deviation	Skewness		
				Statistic	Std. Error	Skewness Coefficient
A20IJ 4	71	5.23	1.50	-.164	.285	-0.57464
A20IJ 5	77	5.47	1.23	.251	.274	0.914633
A20IJ 6	189	5.76	1.45	-.305	.177	-1.72293
A20IJ 7	92	5.68	1.45	-.465	.251	-1.84952
PPP_O_Support_G1	67	47.96	14.78	-1.433	.293	-4.89275
PPP_O_Support_G2	148	54.95	9.68	-1.883	.199	-9.44772
PPP_O_Support_G3	114	55.74	9.54	-2.124	.226	-9.37752
PPP_O_Support_G4	75	52.63	12.80	-1.610	.277	-5.80367
PPP_O_Support_G5	104	52.44	11.85	-1.557	.237	-6.57616
PPP_O_Support_G6	199	54.00	11.23	-1.843	.172	-10.6952
PPP_O_Support_G7	89	52.75	14.10	-2.241	.255	-8.77445
PPP_P_Support_G1	67	50.55	16.62	-1.952	.293	-6.66445
PPP_P_Support_G2	148	48.80	18.00	-1.681	.199	-8.43011
PPP_P_Support_G3	114	46.58	20.79	-1.428	.226	-6.30408
PPP_P_Support_G4	75	50.63	16.77	-1.966	.277	-7.08562
PPP_P_Support_G5	104	48.47	18.95	-1.591	.237	-6.71726
PPP_P_Support_G6	199	47.16	20.86	-1.398	.172	-8.11379
PPP_P_Support_G7	89	45.40	21.86	-1.297	.255	-5.07904

Note. From BB. H1.FINAL.noabuse.1_11_14.sav

Specific Aim 1, Confirmatory Factor Analysis

The first aim of this project was to identify the latent variables in the BabyBEEP dataset relating to stress, depression, and social support through confirmatory factor analysis (CFA). CFA is the first step in structural equation modeling. The most basic form of CFA is a simple correlation. Each manifest variable was evaluated for skewness using original values (Table 4.4) in order to determine whether correlations should be measured with parametric (Pearson's r) or non-parametric (Spearman's rho) tests.

Skewness is a measure of how symmetrical, or how normally distributed the data is around the mean. The manifest variables that the latent Stress construct loaded to were both generally not skewed; their skewness values were less than 2.5 times the standard

error of skewness, a common limit of acceptable skew (Meyers, Gamst, & Guarino, 2005) except in groups 5 and 6. Thus Pearson's correlation coefficient was used to calculate correlations for this construct, presented in Table 4.13. Depression demonstrated a similar pattern of skewness, only demonstrating significant skew in group 6 and 7 (Table 4.8). Social Support (Table 4.9) was significantly skewed, as were the Cotinine measurements (Table 4.10-12). For the skewed variables, Spearman's rho was utilized in the calculation of correlations.

The latent variable, Stress, loaded to "perceived life stressors" (PPP_Stress) and "perceived stress/anxiety" (PSA). As noted in Table 4.7, these two variables were always significantly ($p< 0.000$) moderately correlated (Pearson's $r =0.336$-0.563).

The second latent variable, Depression, loaded to the Mental Health Inventory 5 (MHI5) and "sense of uselessness or worthlessness" (A20IJ). These correlations (Table 4.8) were also significantly ($p<0.000$) moderately correlated at every time point (Spearman's rho = 0.433-0.601).

Table 4.7

Correlations between Perceived Life Stressors and Perceived Stress and Anxiety

		Perceived Stress and Anxiety						
		1	2	3	4	5	6	7
Perceived Life Stressor								
1	Pearson Correlation	**.394****	.[a]	.[a]	.[a]	.232	.034	.375
	Sig. (2-tailed)	.000				.217	.829	.078
	N	100	0	0	0	30	42	23
2	Pearson Correlation	.[a]	**.435****	.[a]	.[a]	.131	.162	.426**
	Sig. (2-tailed)		.000			.319	.100	.004
	N	0	219	0	0	60	104	45
3	Pearson Correlation	.[a]	.[a]	**.393****	.[a]	.362*	.428**	.304*
	Sig. (2-tailed)			.000		.026	.000	.033
	N	0	0	175	0	38	82	49
4	Pearson Correlation	.[a]	.[a]	.[a]	**.328****	.032	.065	.326
	Sig. (2-tailed)				.000	.880	.611	.104
	N	0	0	0	121	25	64	26
5	Spearman's rho	.030	.234	.170	.410*	**.453****	.316	
	Sig. (2-tailed)	.874	.071	.309	.042	.000	.684	
	N	30	60	38	25	161	4	0
6	Spearman's rho	.230	.289**	.404**	.188	.600	**.463****	
	Sig. (2-tailed)	.143	.003	.000	.136	.400	.000	
	N	42	104	82	64	4	296	0
7	Pearson Correlation	.304	-.001	.145	.229	.[a]	.[a]	**.459****
	Sig. (2-tailed)	.158	.994	.319	.260			.000
	N	23	45	49	26	0	0	143

Notes: Computed from BB.H1.FINAL.1_19_14.sav Unless noted as Spearman's rho, the correlation coefficient is Pearson's r.

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

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

a. Cannot be computed because at least one of the variables is constant.

Table 4.8

Correlations between MHI-5 and Sense of Worthlessness

			Sense of Worthlessness (A20IJR)						
Group			1	2	3	4	5	6	7
MHI-5	1	Correlation Coefficient	**.583****	.[a]	.[a]	.[a]	.446*	.288	.627**
		Sig. (2-tailed)	.000				.015	.064	.002
		N	95	0	0	0	29	42	21
	2	Correlation Coefficient	.[a]	**.483****	.[a]	.[a]	.247	.535**	.246
		Sig. (2-tailed)		.000			.059	.000	.117
		N	0	207	0	0	59	100	42
	3	Correlation Coefficient	.[a]	.[a]	**.585****	.[a]	.673**	.523**	.343*
		Sig. (2-tailed)			.000		.000	.000	.017
		N	0	0	169	0	38	82	48
	4	Correlation Coefficient	.[a]	.[a]	.[a]	**.454****	.323	.428**	.540**
		Sig. (2-tailed)				.000	.115	.001	.004
		N	0	0	0	117	25	62	26
	5	Correlation Coefficient	.270	.194	.656**	-.200	**.431****	.908	.[a]
		Sig. (2-tailed)	.149	.137	.000	.338	.000	.092	
		N	30	60	38	25	159	4	0
	6	Spearman's rho	.447**	.371**	.377**	.418**	.800	**.546****	
		Sig. (2-tailed)	.003	.000	.000	.001	.200	.000	
		N	42	104	82	64	4	295	0
	7	Spearmans's rho	.441*	.192	.352*	.263			**.597****
		Sig. (2-tailed)	.035	.207	.013	.195			.000
		N	23	45	49	26	0	0	143

Notes: Computed from BB.H1.FINAL.1_19_14.sav. Unless noted as Spearman's rho, the correlation coefficient is Pearson's r.
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
a. Cannot be computed because at least one of the variables is constant.

The third latent variable, Social Support, was comprised of measures of two completely separate sources of support, that from their partners, and the support from other people. Not surprisingly these variables were not consistently correlated (Table

4.9). They did demonstrate very small correlations throughout the gestational time periods, which were significant for four of the groups.

Table 4.9

Correlations between Partner Support and Other Support

			Partner Support						
Groups			1	2	3	4	5	6	7
Other Support	1	Correlation Coefficient	**-.006**				-.171	.162	.090
		Sig. (2-tailed)	.956				.366	.306	.684
		N	100	0	0	0	30	42	23
	2	Correlation Coefficient		**.196****			.193	.045	.168
		Sig. (2-tailed)		.004			.140	.649	.269
		N	0	219	0	0	60	104	45
	3	Correlation Coefficient			**.028**		.132	.204	.136
		Sig. (2-tailed)			.714		.428	.065	.352
		N	0	0	175	0	38	82	49
	4	Correlation Coefficient				**.214***	.069	-.015	.210
		Sig. (2-tailed)				.019	.744	.905	.302
		N	0	0	0	121	25	64	26
	5	Correlation Coefficient	-.021	.069	.062	.156	**.164***	0.000	
		Sig. (2-tailed)	.914	.603	.713	.458	.038	1.000	
		N	30	60	38	25	161	4	0
	6	Correlation Coefficient	.035	.120	.003	.206	.400	**.226****	
		Sig. (2-tailed)	.828	.226	.975	.103	.600	.000	
		N	42	104	82	64	4	296	0
	7	Correlation Coefficient	.347	.014	-.167	.264			**.095**
		Sig. (2-tailed)	.105	.928	.253	.193			.258
		N	23	45	49	26	0	0	143

Notes: Computed from BB.H1.FINAL.1_19_14.sav, using Spearman's rho.

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

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

a. Cannot be computed because at least one of the variables is constant.

Table 4.10

Correlations between Cotinine and Perceived Stress/Anxiety

		Cotinine						
Groups		1	2	3	4	5	6	7
PSA								
1	Correlation Coefficient	.189	.055	.239	.331*	.274*	.227	.193
	Sig. (2-tailed)	.537	.769	.098	.014	.034	.109	.184
	N	13	31	49	55	60	51	49
2	Correlation Coefficient	.120	.025	-.106	-.164	-.016	-.186	-.009
	Sig. (2-tailed)	.467	.833	.322	.089	.878	.087	.934
	N	39	71	90	108	98	86	95
3	Correlation Coefficient	-.106	-.095	-.054	.015	.171	.159	-.082
	Sig. (2-tailed)	.586	.458	.624	.884	.118	.164	.444
	N	29	63	84	99	85	78	90
4	Correlation Coefficient	-.054	.088	.141	.100	.054	.236	.232
	Sig. (2-tailed)	.843	.595	.296	.446	.692	.118	.112
	N	16	39	57	60	57	45	48
5	Correlation Coefficient	.181	-.122	.098	.008	-.015	.015	.014
	Sig. (2-tailed)	.519	.460	.494	.947	.901	.914	.912
	N	15	39	51	67	68	51	66
6	Correlation Coefficient	.005	-.072	.015	-.201*	-.113	-.032	.044
	Sig. (2-tailed)	.973	.488	.866	.015	.205	.733	.629
	N	44	94	133	146	128	118	122
7	Correlation Coefficient	-.054	-.151	-.070	.133	.117	.020	-.128
	Sig. (2-tailed)	.799	.301	.573	.261	.332	.886	.328
	N	25	49	68	73	71	55	60
8	Correlation Coefficient	.	.100	.000	-.714	-1.000**	.300	1.000**
	Sig. (2-tailed)	.	.873	1.000	.111	.	.624	.
	N	0	5	4	6	2	5	2

There were not any significant within group correlations between cotinine and perceived stress/anxiety (Table 4.10). Cotinine is moderately correlated with perceived life stressors in Group 1, but not at any other time in the study (Table 4.11), and it is not correlated with depression as measured by the MHI-5 (Table 4.12)

Table 4.11

Correlations between Cotinine and Perceived Life Stressors

		Cotinine							
		1	2	3	4	5	6	7	8
PPP_Stress									
1	Correlation Coefficient	.632*	.157	.205	.195	.245	.164	.215	-.041
	Sig. (2-tailed)	.021	.398	.157	.155	.059	.249	.137	.805
	N	13	31	49	55	60	51	49	38
2	Correlation Coefficient	.262	-.019	-.158	-.146	.021	-.017	.091	-.160
	Sig. (2-tailed)	.108	.873	.136	.132	.836	.876	.383	.247
	N	39	71	90	108	98	86	95	54
3	Correlation Coefficient	-.269	-.009	-.101	-.027	.071	.121	-.142	.078
	Sig. (2-tailed)	.159	.942	.359	.794	.518	.290	.182	.558
	N	29	63	84	99	85	78	90	59
4	Correlation Coefficient	-.068	.028	.083	-.099	-.035	.018	-.028	.176
	Sig. (2-tailed)	.802	.867	.541	.454	.795	.908	.850	.253
	N	16	39	57	60	57	45	48	44
5	Correlation Coefficient	-.020	-.095	.139	-.002	.036	.053	-.068	.062
	Sig. (2-tailed)	.944	.567	.329	.990	.771	.710	.590	.714
	N	15	39	51	67	68	51	66	37
6	Correlation Coefficient	-.031	-.205*	-.113	-.142	-.135	.004	-.055	-.124
	Sig. (2-tailed)	.844	.048	.194	.087	.129	.970	.544	.258
	N	44	94	133	146	128	118	122	85
7	Correlation Coefficient	-.013	.152	.052	.268*	.162	.136	.144	.107
	Sig. (2-tailed)	.950	.296	.676	.022	.178	.324	.271	.469
	N	25	49	68	73	71	55	60	48
8	Correlation Coefficient	.	.316	-.316	-.647	-1.000**	-.051	.	-1.000**
	Sig. (2-tailed)	.	.604	.684	.165	.	.935	.	.
	N	0	5	4	6	2	5	2	3

Notes: Computed from BB.H1.FINAL.1_19_14.sav, using Spearman's rho.

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

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

a. Cannot be computed because at least one of the variables is constant.

Table 4.12

Correlations between Cotinine and MHI-5 Across Groups

			Cotinine							
Groups			1	2	3	4	5	6	7	8
MHI-5	1	Correlation Coefficient								
		Sig. (2-tailed)	-.141	.004	-.156	-.202	-.125	-.146	-.185	-.146
		N	.645	.983	.284	.140	.343	.307	.202	.382
	2	Correlation Coefficient	13	31	49	55	60	51	49	38
		Sig. (2-tailed)	.063	-.068	.058	.226*	.051	-.067	-.035	.114
		N	.705	.572	.586	.019	.619	.543	.739	.413
	3	Correlation Coefficient	39	71	90	108	98	86	95	54
		Sig. (2-tailed)	-.011	.167	-.006	.025	-.066	-.124	.030	-.011
		N	.953	.190	.954	.809	.548	.278	.783	.937
	4	Correlation Coefficient	29	63	84	99	85	78	90	59
		Sig. (2-tailed)	-.055	-.268	-.175	-.077	.000	-.099	-.144	-.197
		N	.840	.099	.193	.559	.998	.519	.328	.200
	5	Correlation Coefficient	16	39	57	60	57	45	48	44
		Sig. (2-tailed)	.106	-.030	-.192	.017	-.068	-.240	.052	.051
		N	.706	.854	.177	.893	.584	.090	.680	.766
	6	Correlation Coefficient	15	39	51	67	68	51	66	37
		Sig. (2-tailed)	-.027	.127	.110	.101	.060	.046	.015	.093
		N	.864	.224	.207	.225	.504	.623	.866	.396
	7	Correlation Coefficient	44	94	133	146	128	118	122	85
		Sig. (2-tailed)	-.252	-.099	.069	-.041	.046	.101	.157	-.012
		N	.224	.497	.578	.730	.702	.463	.231	.936
	8	Correlation Coefficient	25	49	68	73	71	55	60	48
		Sig. (2-tailed)	.	-.500	-1.000**	-.314	-1.000**	.600	1.000**	-.500
		N	.	.391	.	.544	.	.285	.	.667

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

Note: Spearman's rho is utilized for these calculations due to the nonparametric cotinine data.

Specific Aim #2

The second specific aim of this project was to identify the linearity of the relationship among tobacco use and the latent constructs of stress, depression, and social support over time. This was performed on both the entire sample, and on the sub-sample of abused women compared to women who did not report abuse currently or within a year of the pregnancy. These results help to determine the feasibility of future latent growth curve analysis, and provide insight into the variation in stress, depression, social support and tobacco use over the course of pregnancy in these groups of women.

The plots are grand mean-centered; the means were calculated for each of the seven groups, and then the mean of those seven means was taken to produce the grand mean. Then the grand mean was subtracted from each subject's values of the variable of interest. The plots in Figure 4.1 illustrate the grand-mean centered latent variable and cotinine means in each of the seven groups, which is a picture of the changing relationship of the latent variables and cotinine over the course of pregnancy. The zero intercept line of these group values with the Y axis is the grand mean, or the expected outcome if a group whose value matched the grand mean. It should be noted that these are not standardized grand mean scores; the Y axis values do not represent z-scores, so the magnitude of differences between variables cannot be inferred by this comparison plot, only trends in linearity and trends away from the grand mean in one direction or another. Negative Y axis scores indicate that the particular group scores fall below the grand mean, and positive scores indicate that the scores are higher than the grand mean.

The overall trends in means plots shown in Figure 4.1 for the total sample are somewhat linear. The widest variation in means occurs in the cotinine group. Smoking starts out in the first trimester (groups 1 and 2) at fairly high levels and decreases dramatically at the 18-23 week group, spikes again at 24 weeks and then decreases in the third trimester. The small sample (n=13) in group 8 showed a marked increase in their cotinine levels after 37 weeks gestation.

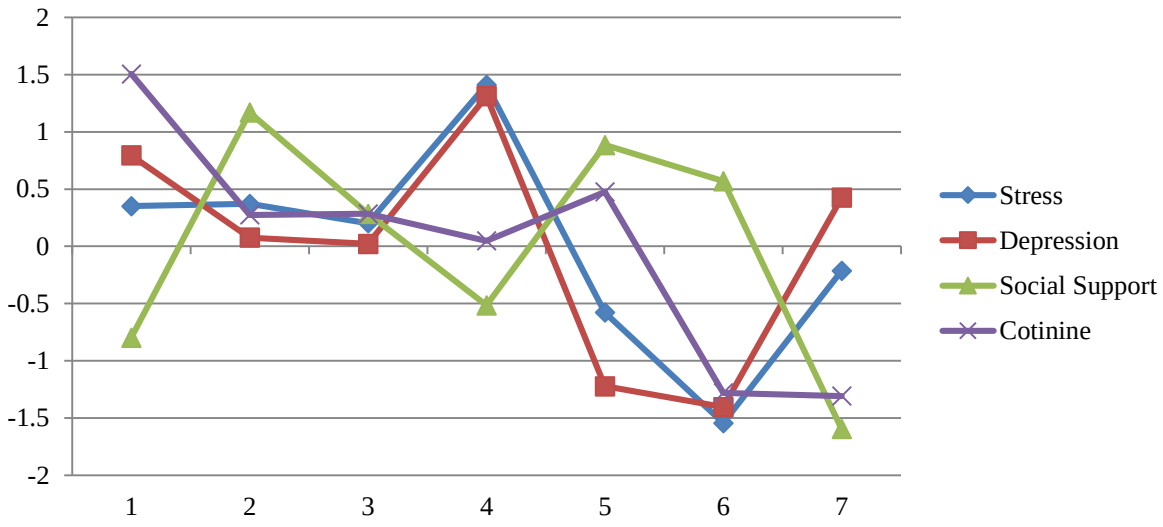

Figure 4.1 Total BB sample standardized means plots for latent variables and cotinine. This plot represents the average of the grand mean centered standardized manifest variables loaded from Stress, Depression and Social Support, along with the grand mean centered Cotinine levels at each time point. From BB.H1.FINAL.1_9_14.sav.

In Figure 4.1, the "lack of depression" score reflects MHI-5 scores and A20IJ scores which were calculated in the typical manner (Rumpf et al., 2001), in which higher scores, and thus higher means on this plot, reflect a lack of depression. These scores strongly mirror the plot for social support in this sample of pregnant women. The nadir of social support and peak depression occurs in group 4, between 19 and 23 weeks of

gestation. Then the peak of social support and nadir of depression occurs immediately following this, in group 5, from 24 to 28 weeks. Both social support and lack of depression decrease slightly again in group 6, from 29 to 31 weeks, reaching their second lowest point in group 7, from 32 to 36 weeks of pregnancy. The lack of standardization among these variables creates the impression that there is less variation in the latent variable scores than in the cotinine. The variable-specific comparison of abused versus not abused women in Figures 4.4-4.7 more clearly show the variation in the group grand mean-centered means.

In contrast to the other variables in Figure 4.1, the average stress experienced in this total sample does not vary much from the grand mean throughout the course of the pregnancy. There is a slight elevation in the amount of stress in group 4, (19-23 weeks) compared to other groups, but overall the results across groups hold close to the grand mean.

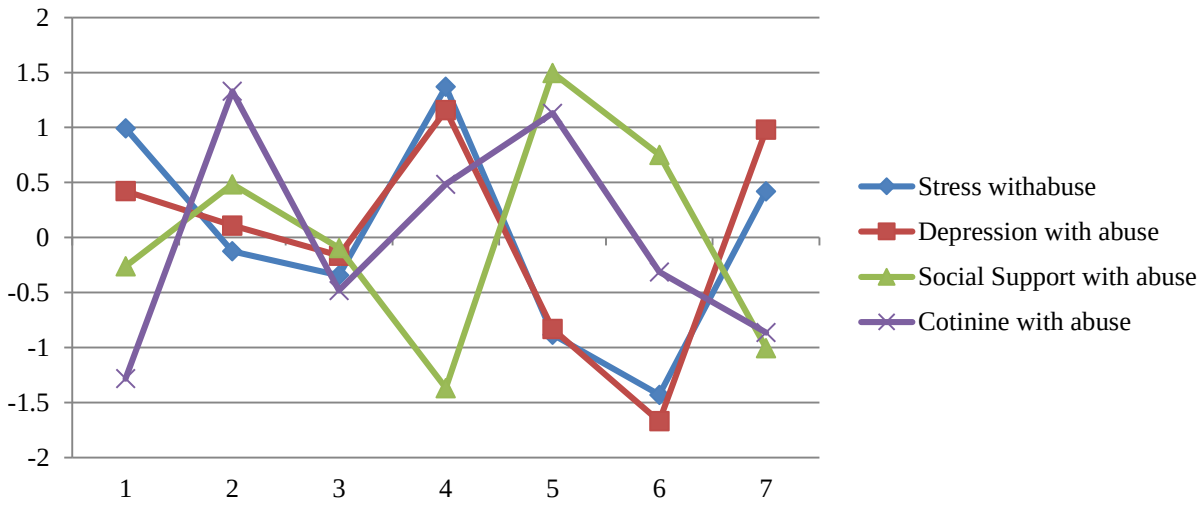

Figure 4.2 Means plots for abused women only. This plot represents the average of the grand mean centered standardized manifest variables loaded from Stress, Depression and Social Support, along with the grand mean centered Cotinine levels at each time point for the subsample of abused women. From BB.H2.FINAL.abused.1_9_10.sav

For the women reporting current abuse (Figure 4.2), the overall patterns for cotinine and the latent variables mirror the patterns in the total population. This group of women report less social support than the grand mean at all time points. Their "lack of depression" means diverge slightly from the pattern in social support at group 6 (19-32 weeks) when social support levels are decreased compared to the previous mean, but there is less depression than in the previous time period. Not surprisingly, their stress levels are consistently above the grand mean, which is more easily seen in Figure 4.7.

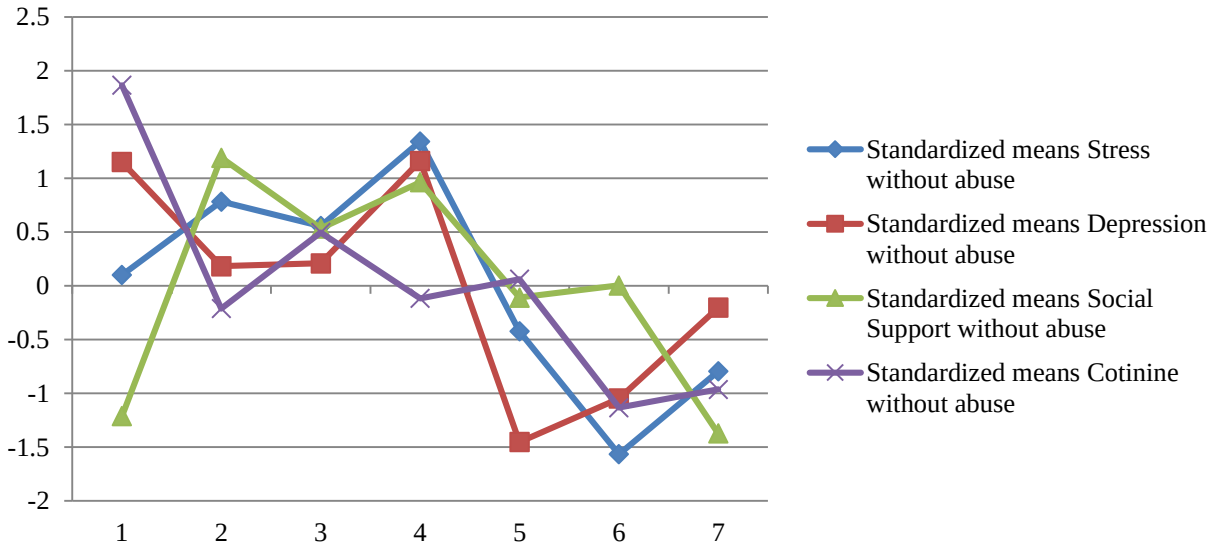

Figure 4.3 Means plots for Women who are not abused. This plot represents the average of the grand mean centered standardized manifest variables loaded from Stress, Depression and Social Support, along with the grand mean centered and standardized Cotinine levels at each time point for women who are not abused. From BB.H2.FINAL.not abused.1_9_10.sav.

The women who report they are not abused also have cotinine levels that mirror the combined sample's somewhat linear plot (Figure 4.3). The lowest points for social support in this group is in the first group (4-9 weeks), and the latter two groups' (after 32 weeks) means. Overall, social support for this subsample is above the grand mean. In

general, this group also has less depression. Their stress scores closely reflect the grand mean until group 5 (24-28 weeks) and continues a very slight dip below the grand mean in group 6 (29-31) weeks before moving back towards the grand mean at the end of pregnancy.

Figure 4.4 compares the cotinine means plots for abused versus not abused women in the sample. It is interesting that the abused group has a very linear decrease in cotinine across the study, with a steeper slope than seen in the group of women who were not abused.

Social support differences between the abused and the not abused women are demonstrated in Figure 4.5. In all time periods, the abused women reported

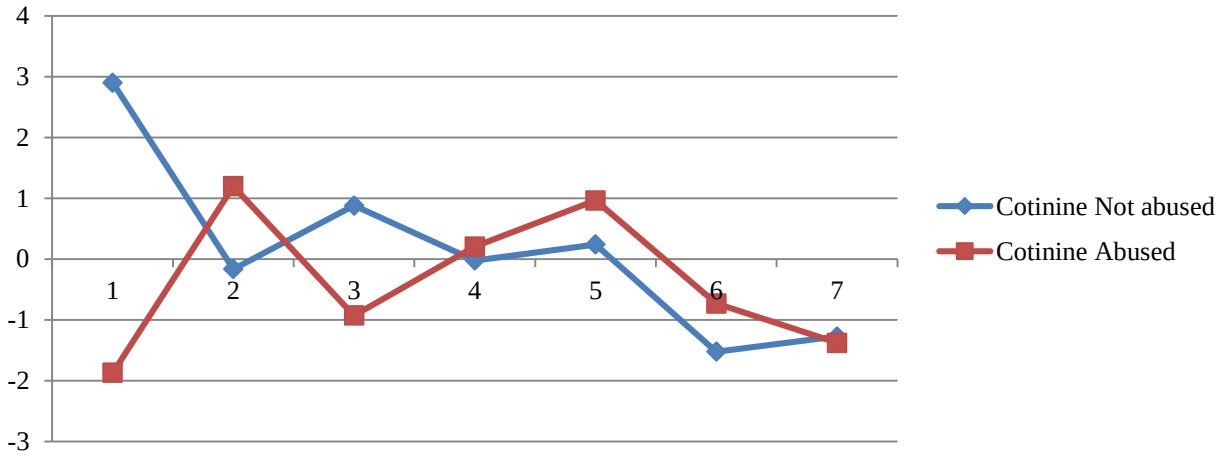

Figure 4.4 Comparison of cotinine means in abused versus not abused women using the total sample grand means. This plot represents the average of the grand mean centered cotinine levels, as measured in saliva, across all time points. From BB.H1.FINAL.1_9_14.sav

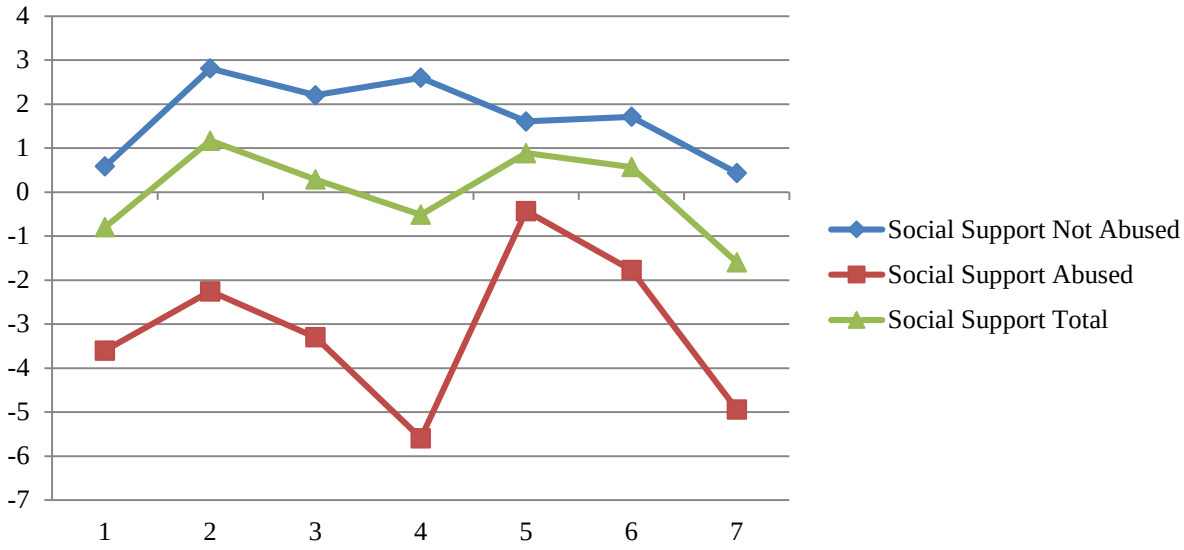

Figure 4.5 Comparison of perceived social support means in abused versus not abused women using the total sample grand means. This plot represents the average of the grand mean-centered latent variable of social support. The values were obtained by summing grand mean-centered values for the PPP Partner Support and PPP Other Support subscales, and dividing by two. From BB.H1.FINAL.1_9_14.sav.

less social support than their not abused counterparts. The drop in social support in Group 4 (19-23 weeks) which is noted in Figure 4.1 is revealed in Figure 4.5 as solely attributed to a drop in perceived support by the abused women. Other than this one time point, the linear plots for social support reflect similar direction of change, in both groups, though there is consistently less social support reported for the abused group and the variance appears greater in the abused group as well.

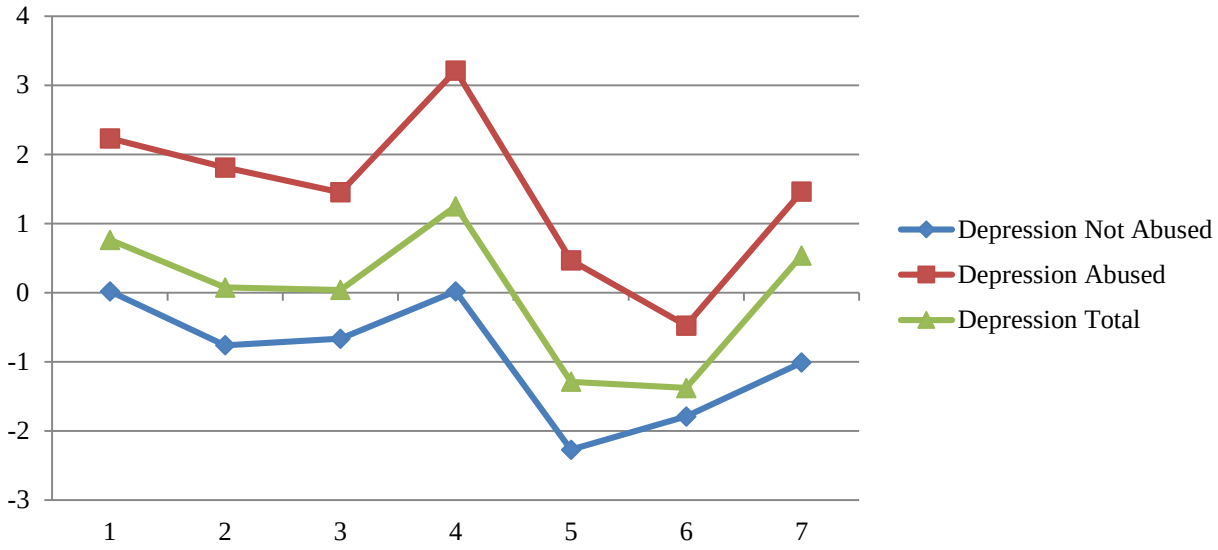

Figure 4.6 Comparison of depression means in abused versus not abused women. This plot represents the average of the grand mean-centered latent variable of depression. The coded values were obtained by summing grand mean-centered values for the MHI-5 and A20I&J and dividing by two. This is a comparison of the split group from the standardized grand means from BB.H1.FINAL.1_10_14.sav.

Regarding the comparison of linear plots for depression shown in Figure 4.6, the changes over time in the abused and not abused populations mirror each other in direction, at all but one time point. For group 6 (29-31 weeks) the abused women appear to be less depressed than in group 5 (24-28 weeks), while the women who are not abused have a slight increase in depression towards the grand mean.

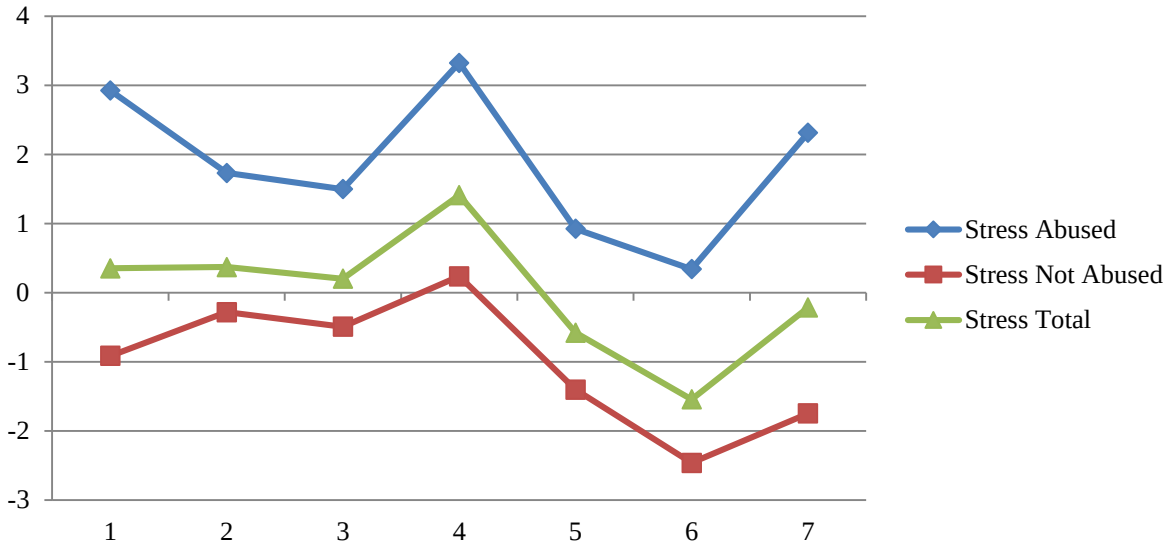

Figure 4.7 Comparison of stress means in abused versus not abused women. This plot represents the average of the grand mean-centered latent variable of stress. The coded values were obtained by summing grand mean-centered values for the PPP Stress subscale and the Perceived Stress & Anxiety measure,then dividing by two. From BB.H1.FINAL.1_10_14.sav.

The linear stress plots shown in Figure 4.7 demonstrates that the difference between stress for abused women and for those not abused is in amplitude, not timing. Both plots for abused and not abused women mirror the total plot in terms of direction change, with a slightly steeper slope in the abused category.

In summary, the means plots for the variables under investigation are generally not linear. The most linear plot is for cotinine values. Furthermore, these plots reveal a distinct difference in amounts of perceived social support, depression and stress between the group of abused and the group of not abused women. And the abused women appear have higher cotinine levels throughout pregnancy, than women who are not abused.

Specific Aim #3

The third specific aim of this dissertation was to determine the associations of tobacco use and latent variables (social support, stress, and depression), at different gestational ages and their impact on gestational length and birthweight. This was to be done through the evaluation of the full structural equation model, *Latent Social Support Model,* of the entire BabyBEEP dataset. In addition, this aim included determining if there were differences in patterns of stress, depression, tobacco use and social support impact across time on gestational length and birthweight during pregnancies of women currently experiencing abuse compared to those not experiencing abuse. All path weights presented below are in standardized units.

The full path model evaluated whether or not the model produced an estimated population covariance matrix that was consistent with the sample covariance matrix. When comparing two models, the differences in closeness of fit of the covariance matrices determines, through evaluation of chi-square changes, whether the sample (data) covariance matrix fits one model significantly better than the other.

Hypothesis #1

The first model evaluation conducted using SEM with OpenMX (Boker et al., 2012) tested the hypothesis that there are differences in impact on the dependent variables of gestational length and birthweight at different times in pregnancy. Restructured groups contained missing data that was managed using full information maximum likelihood procedures. Model fit was evaluated using minus 2 log likelihood (-2LL) and Akaike Information Criterion (AIC). For each latent variable, model

identification was established by fixing the loading of the indicators at 1.0. The variance was freely estimated for all manifest variables. In the null model all factor loadings of coefficients and regression coefficients were simultaneously constrained across the groups and tested against the model in which these coefficients were freely estimated (the alternate model). This SEM analysis was conducted using the entire BabyBEEP sample.

The overall models for birthweight and gestational length were both significant with all predictors. These models will be discussed individually in the following subsections.

Hypothesis 1: Birthweight.

Model Fit.

In this phase of the data analysis, two models were tested and compared. The first model comparison was between the full hypothesized model, known as *Latent Social Support Model* represented by Figure 4.8 and the null model, restricted *Latent Social Support Model* (Figure 4.9) , in which all of the predictors were restricted, specifying that there was not a relationship between birthweight and varying levels of the predictors during seven gestational time periods. Model comparison proceeded by removing the latent construct of social support, allowing the predictors of partner support and other support to independently predict birthweight.

Although the optimality conditions were satisfied for these models, meaning that an optimal solution was found, the comparison of the *Latent Social Support Model* model and its' restricted counterpart found significance without converging (Table 4.18).

There is sufficient evidence based upon the *Latent Social Support Model* (Figure 4.8) comparison with its' fully restricted counterpart to warrant rejection of the claim that variation in levels of stress, depression and social support, does not impact birthweight. Variations in birthweight are better explained by examining the predictor variables separately during seven gestational time periods than as a whole. Please note that although the model was sufficiently powered to test the hypotheses, given the small effect sizes found here for individual predictors (which are consistent with the literature), the model is not sufficiently powered to find significance in the individual paths. Thus, although the model found significant path estimates, there could be other predictors that remain insignificant because of sample size and the complexity of the model.

During the evaluation of the measurement model for the first specific aim, the two manifest indicators for this latent construct, the PPP Partner support subscale and the PPP Other support subscale, were not well correlated. To test whether the unreasonable estimates for the latent social support construct might be an artifact from using two uncorrelated manifest variables, a model was run in which these two scales were directly loading as individual predictors to birthweight. This model, known as the *Split Social Support Model* (Figure 4.10), was also significantly different from its' null (Figure 4.11), but the -2LL and AIC for both the full and restricted *Split Social Support Model* were large r than *Latent Social Support Model* (see Table 4.18).

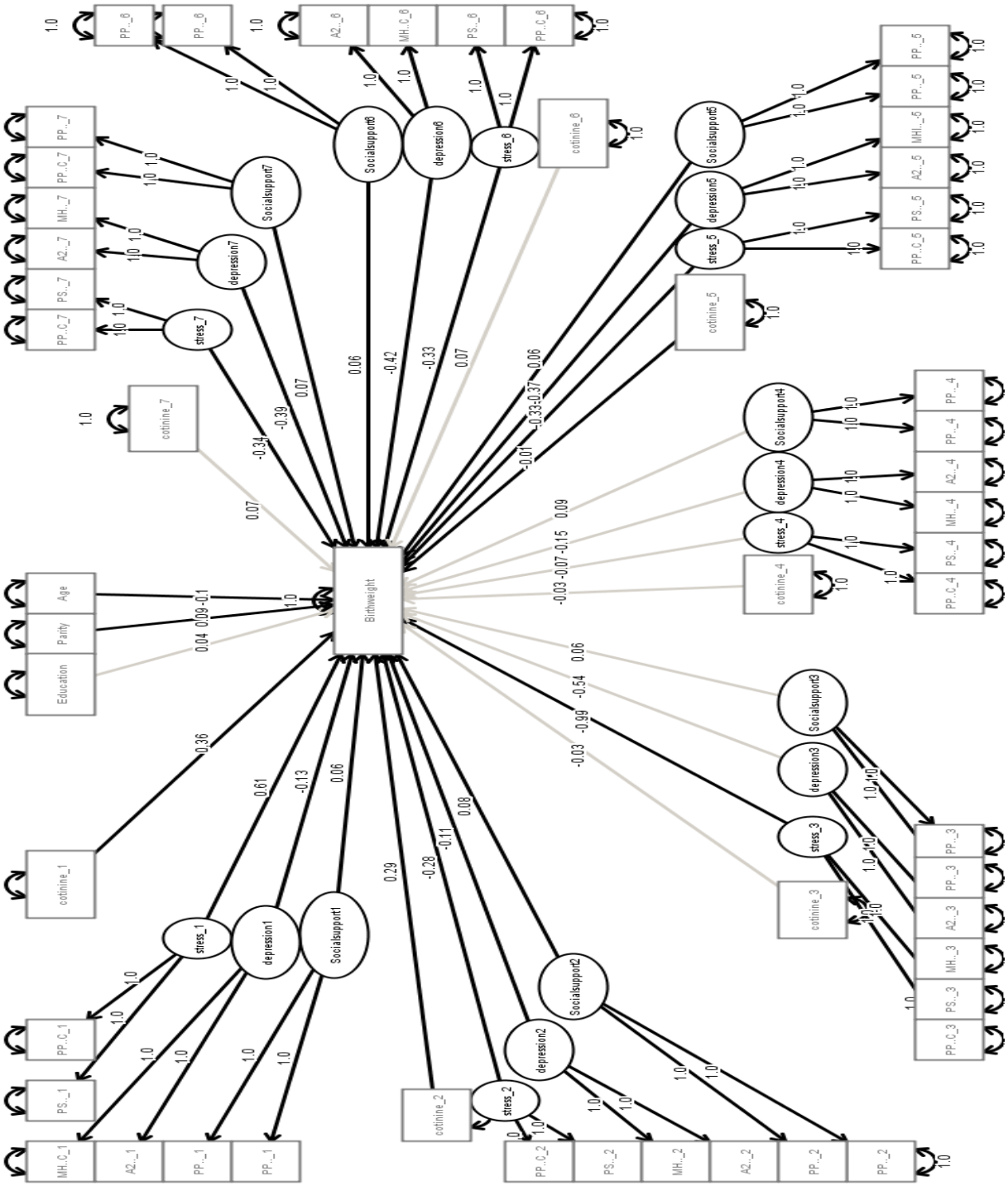

Figure 4.8 The *Latent Social Support Model* for Birthweight. The latent constructs load to manifest variables from all time periods, and the manifest cotinine values are comprised of responses from the entire gestational period. Significant paths are in black ($p<0.01$), non-significant path is in gray. The latent constructs appear in black and the manifest variables are in gray.

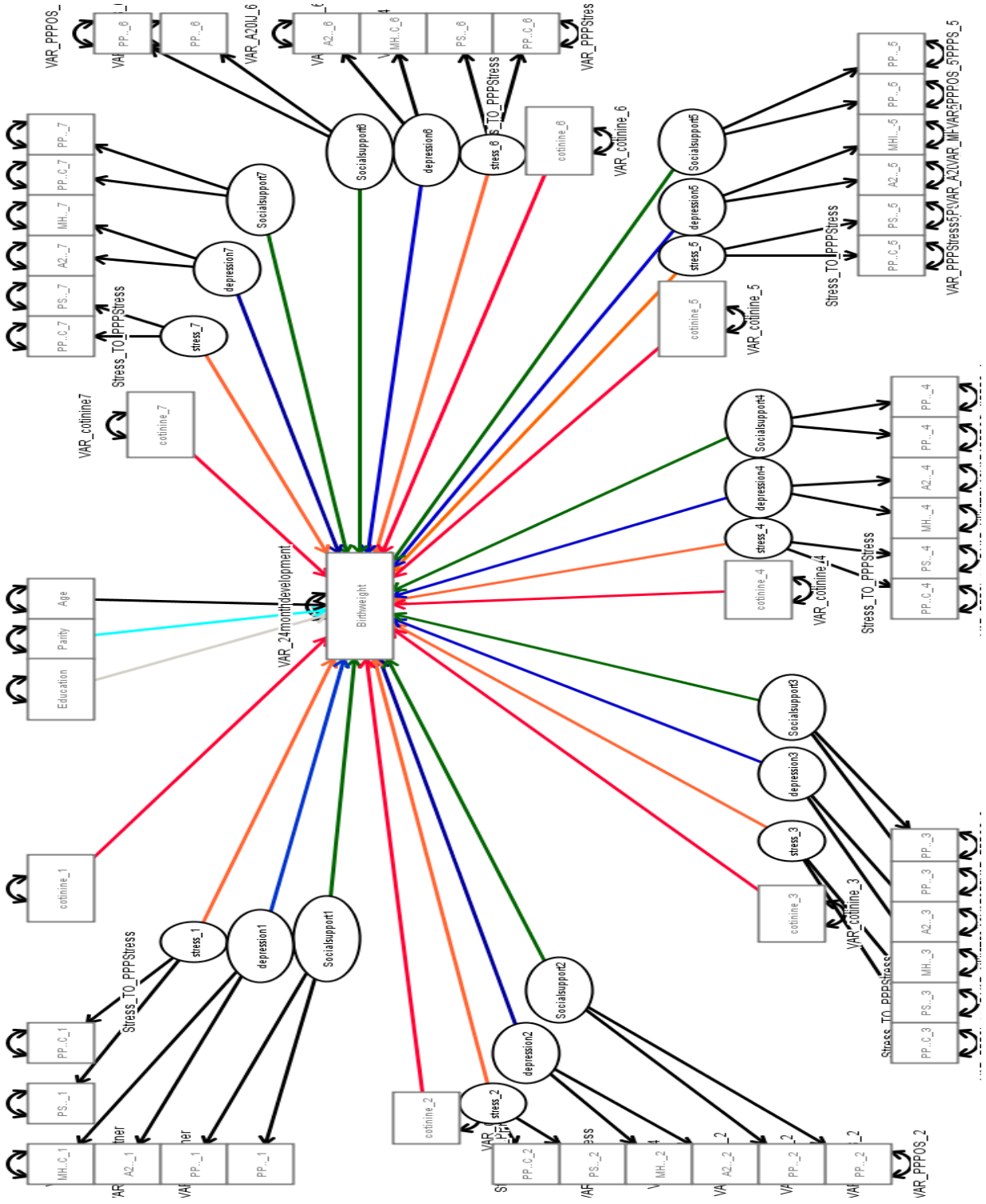

Figure 4.9 The *Latent Social Support Model* Null for Birthweight. The latent constructs path weights from each time period are equal, as signified by matching colors. The latent constructs appear in black and the manifest variables are in gray. All manifest and latent constructs including the outcome variable have variances and there is also a constant to all latents and manifests variables.

While the unrestricted *Latent Social Support Model* establishes that timing of these predictors during pregnancy matters in regard to birthweight, it is not the most parsimonious model for fitting the BabyBEEP data to the model (Table 4.18). The unrestricted *Split Social Support Model* is a slightly better fit. The difference between the two unrestricted models is not significant yet the latter model is a better fit theoretically and methodologically, as the correlations done for Aim #1 have shown that these two kinds of support are not well correlated. Thus the following examination of regression weights is based upon the *Split Social Support Model.*

Table 4.13

Indices of Fit for Total BabyBEEP Birthweight Sample Path Analysis

Model	df	Minus 2 Log Likelihood	AIC	p-value
Restricted Split Social Support Model		32042.55	9058.551	
Split Social Support Model	42	31881.08	9029.081	2.46E-16
Restricted Latent Social Support Model		31945.17	8965.168	
Latent Social Support Model	49	31893.8	9041.802	0.037

Note. p-value is calculated based upon change chi-square of -2 Log Likelihood

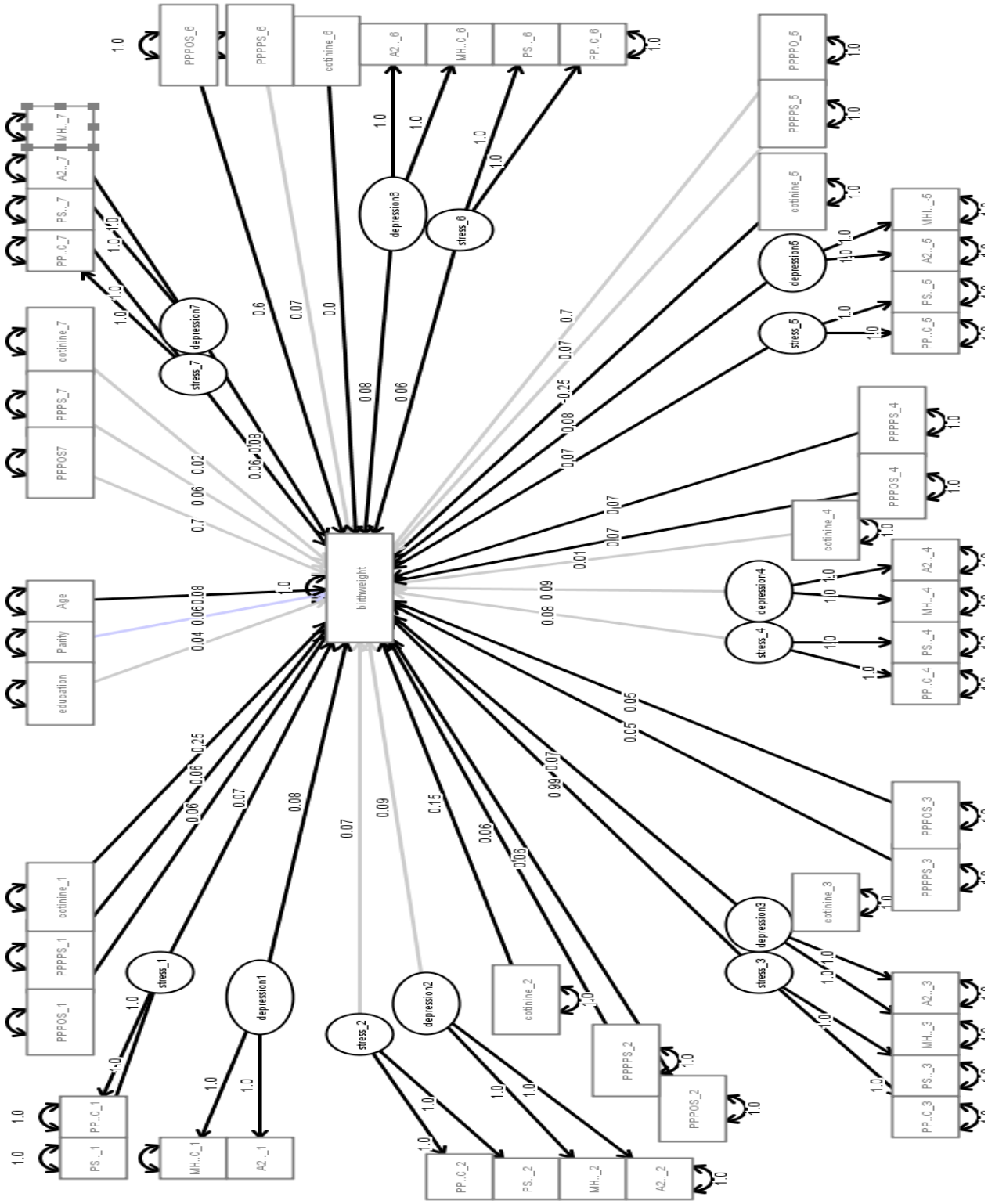

Figure 4.10 Social Support Split Model for birthweight with significant path weights in black, nonsignificant pathweights are in gray. Manifest variables are in gray and latent constructs are in black. Values of variance are not included. From: Birthweight.ONYXmodel with path weights.12_27_13.xml

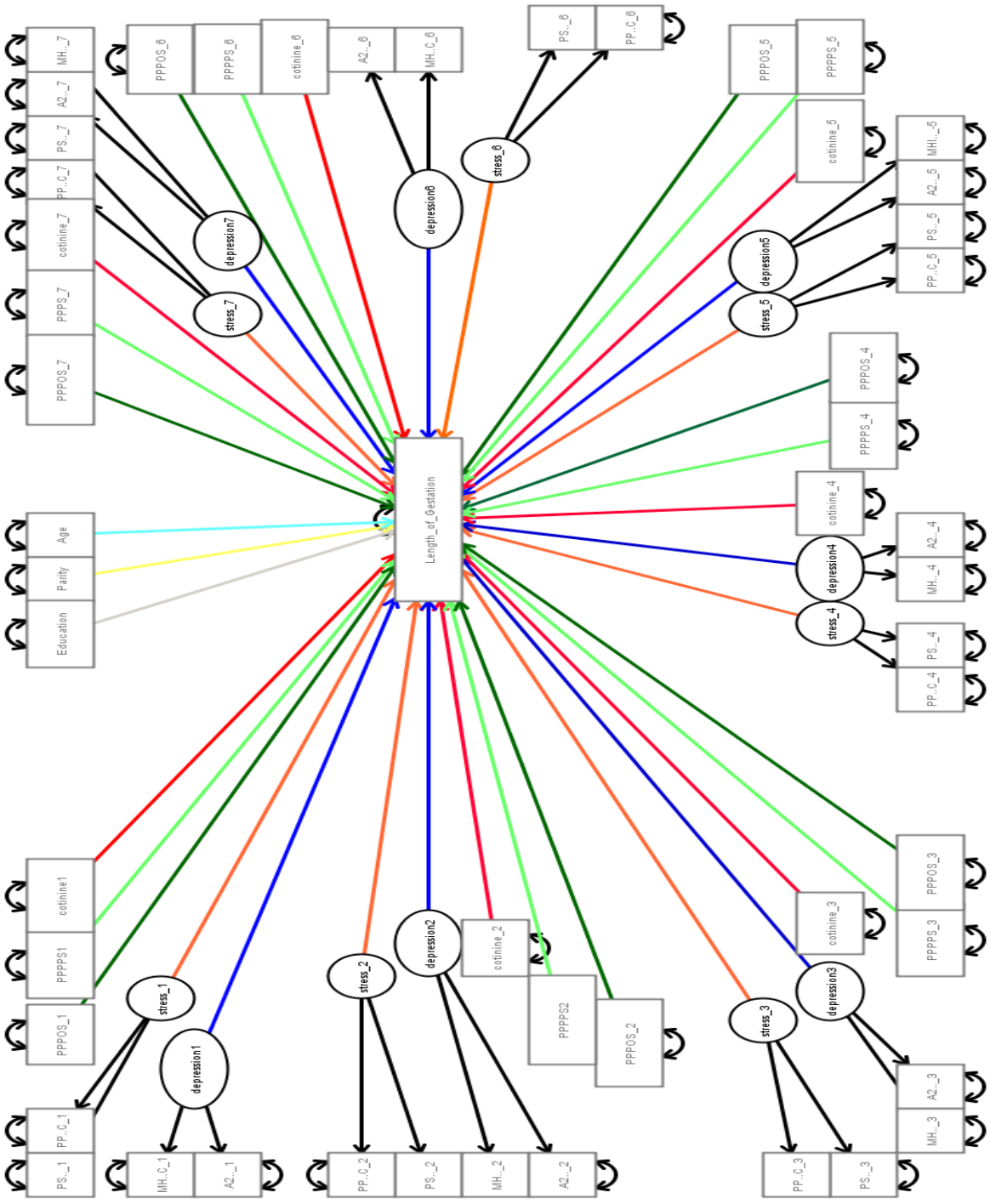

Figure 4.11 Social Support Split Null Model for Birthweight. The latent constructs path weights from each time period are equal, as signified by matching colors. The latent constructs appear in black and the manifest variables are in gray. All manifest and latent constructs including the outcome variable have variances and there is also a constant to all latents and manifests variables.

Regression Weights for Birthweight.

The parameter estimates produced by this modeling reflect the use of Maximum Likelihood estimation. This technique maximizes the likelihood that the sample population data in BabyBEEP could be a representative sample of the population covariance matrix. Unstandardized parameter estimates are regression coefficients. These are the coefficient of X; the slope of the regression line indicating how much Y(dependent variable) changes for each one-unit change in X. The magnitudes of these coefficients are not standardized, and cannot be compared across different types of variables. To accomplish that comparison, the standardized parameter estimates, also known as beta weights are employed. If the parameters are standardized, a one standard deviation change in X °equals Bº (the beta coefficient) standard deviations in Y. Standardizing the coefficients allows this direct assessment among all predictors of the dependent variable. The absolute values of the respective beta weights of the different predictors in the model indicate the predictors that are relatively more or relatively less important in predicting the criterion variable.

The individual variable path estimates loading to birthweight will be examined for both the *Split Social Support Model* and the *Latent Social Support Model* for the purpose of comparison. The completely restricted *Latent Social Support Model* for birthweight demonstrated two significant paths; decreased cotinine was associated with increased birthweight (p=7.24E-4), and increased depression was associated with increased birthweight (p=0.016). In the completely restricted *Split Social Support Model* cotinine remained a significant predictor of birthweight (p=6.65E-4). Also, decreased social

support from others had was associated with increased birthweight (p=0.017). Depression almost achieved significance (p=0.059) in this model as a positive direct effect.

The standardized estimates for the unrestricted *Latent Social Support Model* are presented in Figure (4.12) to allow the reader to judge the similarities and divergence between this model and the unrestricted *Split Social Support Model* (Figure 4.13). References to these models should be assumed to refer to the unrestricted models, unless otherwise specified.

Significance of the path estimates was determined by dividing the regression coefficient by the standard error, producing a t statistic. A p-value was calculated for this t statistic based on the degrees of freedom in the model.

Comparison of Standardized Estimates

The *Latent Social Support Model* standardized estimates are presented in Figure 4.12. There are only 2 significant paths in the model, both for Stress. Group 3 appears to be the time when there is least association between any of the predictors and birthweight. Groups 1, 5 and 6 demonstrate the most significant correlations in this model.

Without considering statistical significance, it appears that in both models (Figures 4.12 and 4.13) depression is the predictor that contributes the most to changes in mean birthweight. Clearly when Social Support is not split, this variable appears in some groups to have a sizeable negative influence on birthweight. When social support is split into two types of support the intercepts and "slope" across time are tempered and remain closer to the mean across groups. It is the predictors from the *Split Social Support Model*

that will be examined individually in the following sections. The path estimates are listed in Table 4.14.

The interpretation of the following standardized estimates assumes that any prediction of the dependent variable by the independent variable occurs while controlling for all other variables in the model.

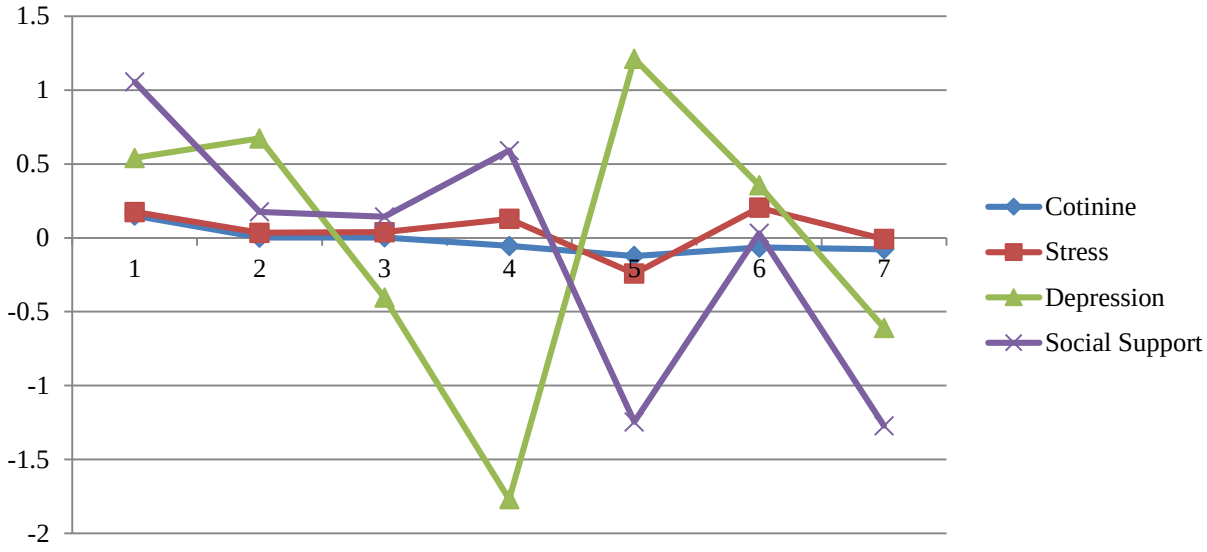

Figure 4.12 Standardized Estimates from *Latent Social Support Model* of latent variables and cotinine loading to birthweight across groups. This is a comparison of the Beta weights for each of these variables as they change across groups. Positive numbers indicate that as the predictor increases by one standard deviation, birthweight increases by the beta weight (standardized estimate) multiplied by the standard deviation of birthweight in the sample (546 grams). Negative numbers indicate that as the predictor increases by one standard deviation, birthweight decreases by beta weight multiplied by the standard deviation of birthweight in the sample. The only significant estimates in this figure are at Stress 5 and 6. From BB.H1.FINAL.1_11_14.csv

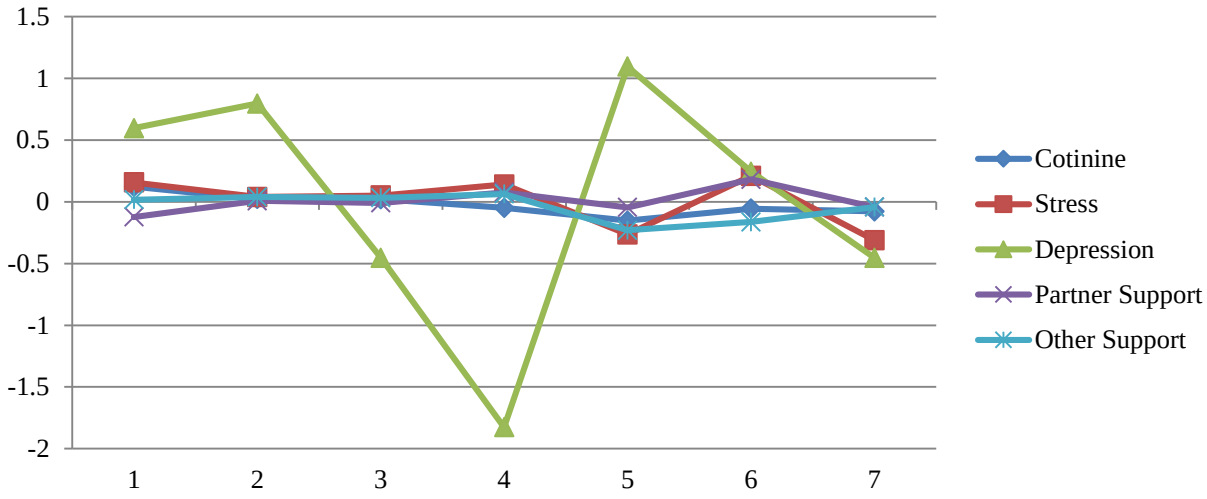

Figure 4.13 Standardized Estimates from the *Split Social Support Model* of latent Stress and Depression Estimates along with manifest predictors for Cotinine, Partner and Other Social Support loading to birthweight across groups. Positive numbers indicate that as the predictor increases by one standard deviation, birthweight increases by the beta weight (standardized estimate) multiplied by the standard deviation of birthweight in the sample (546 grams). Negative numbers indicate that as the predictor increases by one standard deviation, birthweight decreases by beta weight multiplied by the standard deviation of birthweight in the sample.

Table 4.14

Unstandardized and Standardized Path Estimates for Birthweight in the Unrestricted Split Social Support Model

Predictor	Regression Weight	Standard Error	Standardized Beta Weight	Standardized Standard Error	t- statistic
Cotinine_G1	0.123392936	0.12243506	0.12262747	0.12167554	1.00
Cotinine_G2	0.02304124	0.07613642	0.022898304	0.07566411	0.30
Cotinine_G3	0.020698034	0.07852356	0.020569634	0.07803644	0.26
Cotinine_G4	-0.049723976	0.08631045	-0.049415514	0.08577502	-0.57
Cotinine_G5	-0.153515183	0.09627737	-0.152562854	0.09568012	-1.59
Cotinine_G6	-0.056245286	0.09554421	-0.05589637	0.0949515	-0.58
Cotinine_G7	-0.078259023	0.11131944	-0.077773544	0.11062887	-0.70
Stress1	0.251760445	0.23875447	0.156681452	0.14858727	1.05
Stress2	0.059705787	0.12889897	0.039054185	0.08431418	0.46
Stress3	0.080787165	0.17753645	0.050197443	0.11031301	0.45
Stress4	0.247674249	0.24288572	0.140628819	0.1379099	1.01
Stress5	-0.407118012	0.16744673	-0.264032828	0.10859611	-2.43*
Stress6	0.314368942	0.12330292	0.21069481	0.08263948	2.54**
Stress7	0.002807855	0.21072813	0.001884187	0.14140732	0.013
Depression1	0.121017798	0.09055819	0.596614317	0.44376418	1.34
Depression2	0.149945496	0.08211072	0.796864597	0.43650180	1.82
Depression3	-0.030599035	0.06350016	-0.452944252	0.93993482	-0.48
Depression4	-0.229056934	0.1319074	-1.826757333	1.05190510	-1.73
Depression5	0.193148981	0.11540919	1.095938169	0.65478601	1.67
Depression6	0.070119583	0.05318122	0.24427443	0.18498249	1.32
Depression7	-0.030750091	0.06542959	-0.453989928	0.96757678	-0.46
Partnersupport1	-0.1235817	0.11108306	-0.122815063	0.11039396	-1.11
Partnersupport2	0.0081018	0.0666512	0.008051541	0.06623773	0.12

Predictor	Regression Weight	Standard Error	Standardized Beta Weight	Standardized Standard Error	t- statistic
Partnersupport3	-0.008774757	0.0866425	-0.008720323	0.08610501	-0.10
Partnersupport4	0.076982679	0.10554218	0.076505119	0.10488745	0.72
Partnersupport5	-0.045068842	0.0929878	-0.044789258	0.09241095	-0.48
Partnersupport6	0.182644053	0.0672683	0.181511023	0.06685101	2.71**
Partnersupport7	-0.043237781	0.11079512	-0.042969557	0.1101078	-0.39
Othersupport1	0.016820959	0.10778367	0.016716611	0.10711504	0.15
Othersupport2	0.039048491	0.06555878	0.038806255	0.06515208	0.595
Othersupport3	0.033087561	0.08158639	0.032882303	0.08108027	0.40
Othersupport4	0.064470299	0.09790904	0.064070359	0.09730166	0.65
Othersupport5	-0.231977264	0.0835825	-0.230538196	0.083064	-2.77
Othersupport6	-0.164472539	0.06451062	-0.163452236	0.06411043	-2.54
Othersupport7	-0.192200815	0.09993792	-0.1910085	0.09931796	-1.92
Age	-0.079090422	0.0417963	-0.078599786	0.04153701	1.89*
Education	0.029197924	0.04086498	0.029016795	0.04061147	0.71
Parity	0.007564715	0.04009111	0.007517787	0.0398424	0.188

Note. * $p < 0.05$, **$p < 0.01$

Cotinine Estimates Loading to Birthweight.

The path weights for cotinine are graphically depicted in Figure 4.14 and listed in Table 4.14. These path weights were not statistically significant.

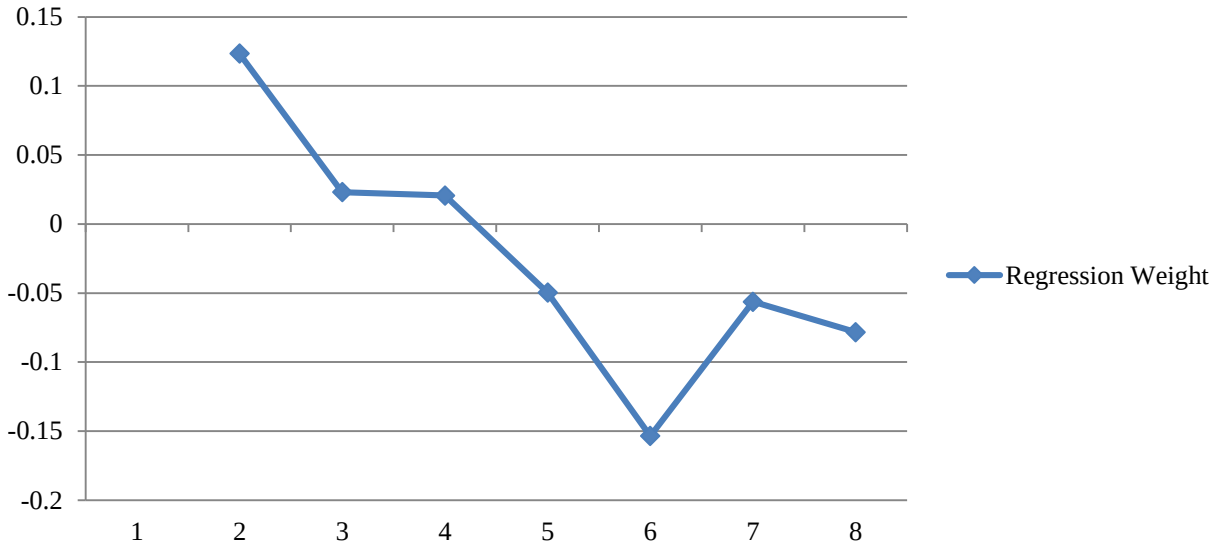

Figure 4.14. Unstandardized Cotinine Estimates from Social Support Split model for loadings to birthweight across Groups Positive numbers indicate that as the predictor increases by one standard deviation, birthweight increases by the beta weight (standardized estimate) multiplied by the standard deviation of birthweight in the sample (546 grams). Negative numbers indicate that as the predictor increases by one standard deviation, birthweight decreases by beta weight multiplied by the standard deviation of birthweight in the sample.

Stress Estimates Loading to Birthweight.

In the *Split Social Support Model*, the regression weights are significant ($p<0.01$) for groups 5 and 6. As depicted in Figure 4.15, the point at which stress has the most impact on birthweight is for Group 5 (24-28 weeks), when there is a negative relationship between stress and birthweight. During this stage of pregnancy, lower stress is associated with higher birthweights. For each increase of one unit in the latent construct of stress for Group 5, there is an average increase in the mean birthweight of 228 grams. In contrast, in Group 6, for each increase of one unit in the latent construct of stress there is an average decrease in the mean birthweight of 172 grams.

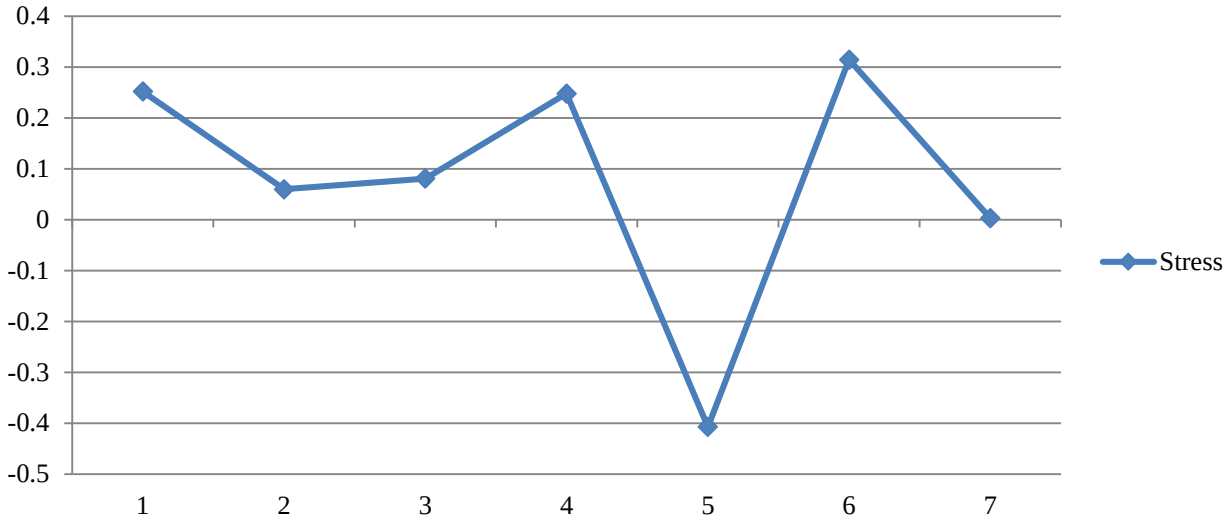

Figure 4.15. Unstandardized Stress Estimates from *Split Social Support Model* for loadings to birthweight across Groups. Only Group 5 and 6 are statistically significant regression estimates.

Depression Path Estimates Loading to Birthweight.

The *Split Social Support Model* depicted in Figure 4.16, did not return statistically significant Depression path estimates for any groups. Groups 4 and 5 approached significance with p-values of 0.08 and 0.09 respectively.

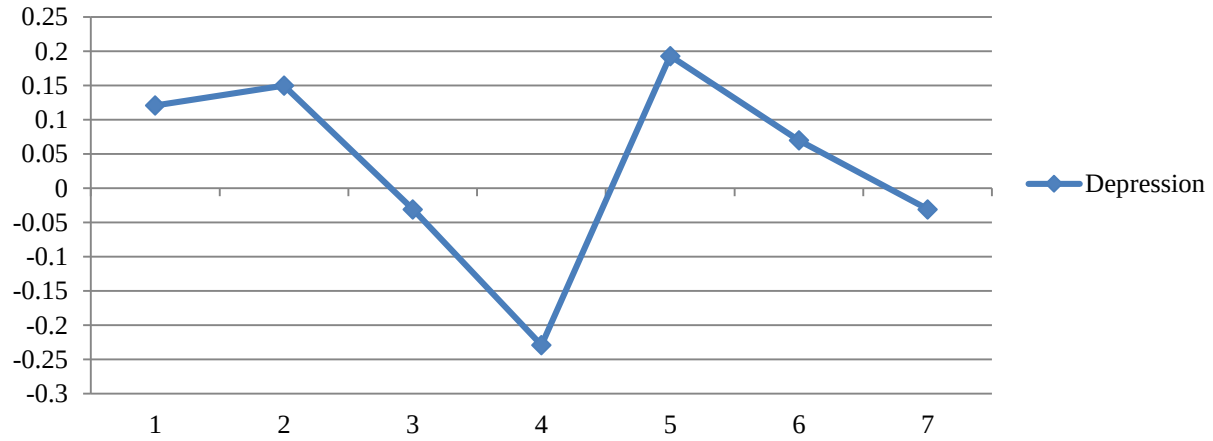

Figure 4.16 Unstandardized Depression Estimates from Social Support Split model for loadings to birthweight across Groups. Groups 2 and 4 are NOT statistically significant estimates.

Social Support Path Estimates Loading to Birthweight.

The *Split Social Support Model* evaluated the predictors of Partner Support and Other Support separately (Figures 4.10, & 4.17). The regression coefficients was significant ($p<0.01$) for Partner Support only at Group 6 (29-32 weeks). The Other Support regression coefficients were significant for groups 5-7 (24-37 weeks). Groups 5 and 6 were significant at the $p<0.01$ level, while group 7 was significant at $p<0.05$.

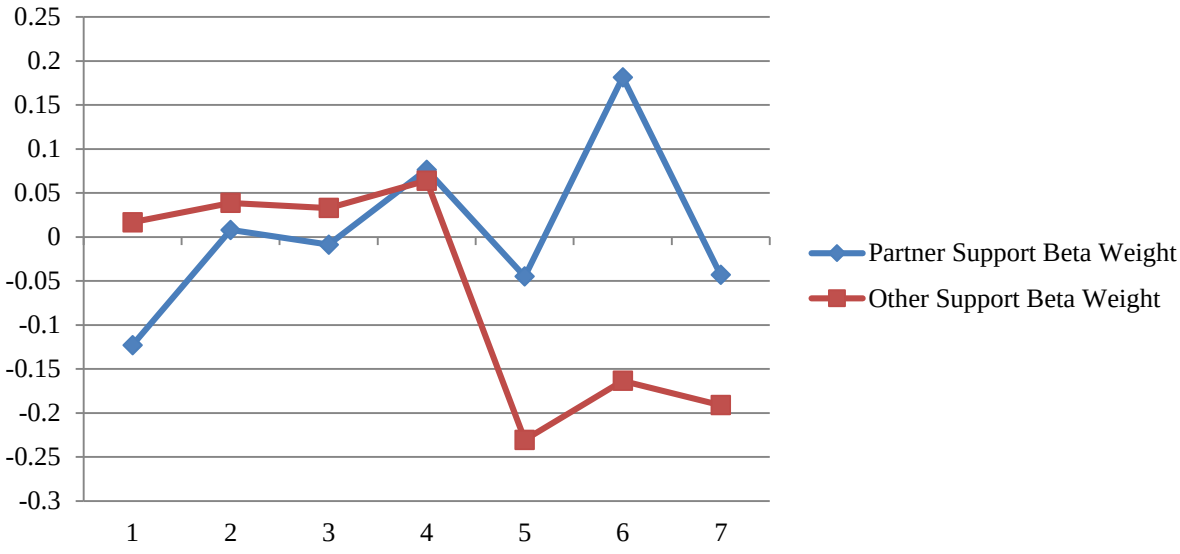

Figure 4.17. Standardized Comparison of Partner and Other Social Support Estimates from the Social Support Split Model for loadings to birthweight across Groups

As a predictor, for every 22 points increase in the PPP Partner Support subscale (Figure 4.18), there is an average increase in mean birthweight of 100 grams in Group 6.

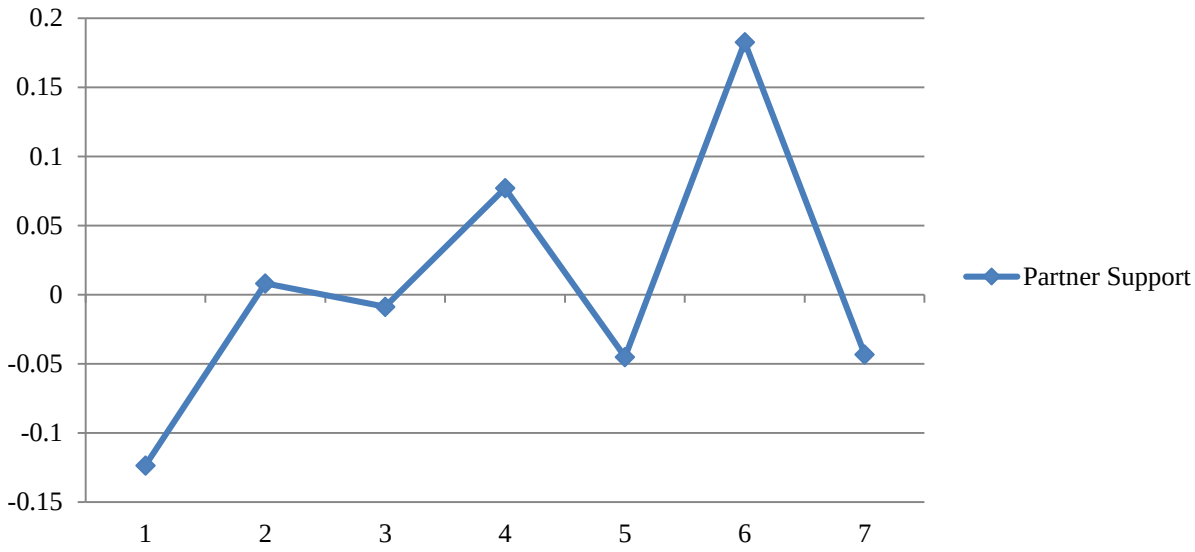

Figure 4.18. Unstandardized Partner Social Support Estimates from the Social Support Split Model for loadings to birthweight across Groups

The effect of Other Social Support was in the opposite direction of that found for partner support. An increase of 13 points in the PPP Other Support subscale (Figure 4.19) in Group 5 was associated with an average decrease in mean birthweight of 127 grams. In Group 6 an increase in 12 points produced an average decrease in mean birthweight of 90 grams. Group 7 had an average decrease in mean birthweight of 105 grams associated with an increase in 15 points on the PPP Other Support subscale.

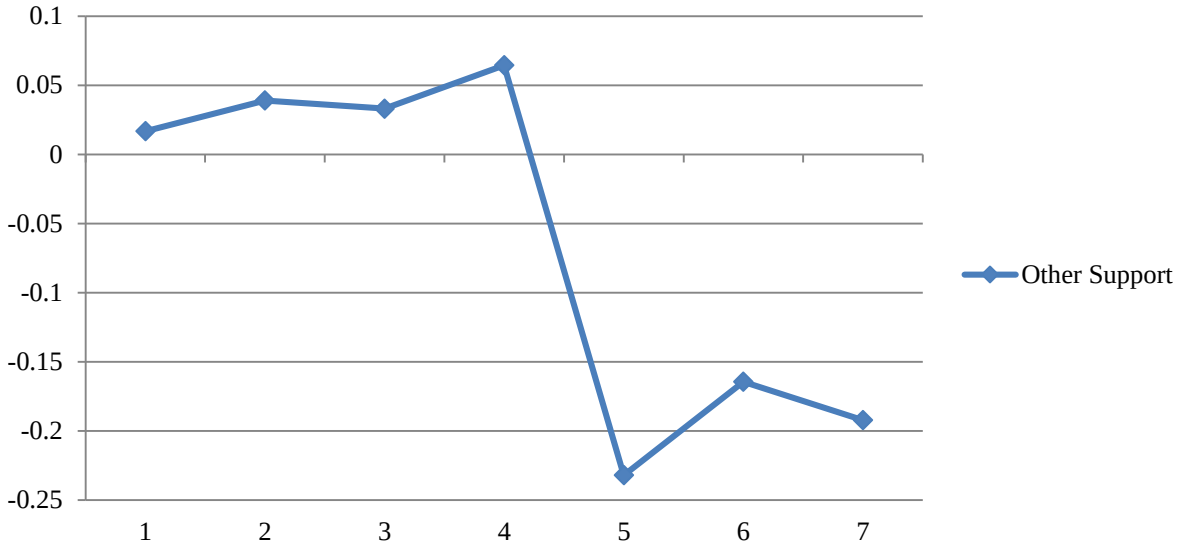

Figure 4.19. Unstandardized Other Social Support Estimates from the Social Support Split Model for loadings to birthweight across Groups

Hypothesis 1: Gestational Length

Model Fit.

In this phase of the data analysis, two specific were tested and compared. The first model comparison was between the full hypothesized model, known as *Latent Social Support Model* represented by Figure 4.20 and the null model, restricted *Latent Social Support Model* (Figure 4.21) , in which all of the predictors were restricted, specifying that the relationship between gestational length and the predictors did not vary across seven gestational time periods. Model comparison proceeded by removing the latent construct of social support, allowing the predictors of partner support and other support to independently predict birthweight.

Although the optimality conditions were satisfied for these models, meaning that an optimal solution was found, the comparison of the full models and restricted models,

for both the *Latent Social Support Model* and the *Split Social Support Model*, found significance without converging (Table 4.15).

Table 4.15

Indices of Fit for Total BabyBEEP Gestational Length sample Path Analysis

Model	df difference	Minus 2 Log Likelihood	AIC	p-value
Restricted Split Social Support Model		32094.42	9084.42	
Split Social Support Model	42	31935.98	9057.97	7.66E-16
Restricted Latent Social Support Model		31994.91	8988.91	
Latent Social Support Model	49	31943.05	9065.04	3.65E -2

Note. p-value is calculated based upon change chi-square of -2 Log Likelihood

There is sufficient evidence based upon the *Latent Social Support Model* (Figure 4.20) comparison with the fully restricted model to warrant rejection of the claim that variation in levels of stress, depression and social support, does not impact gestational length. Variations in gestational length are better explained by examining the predictor variables separately during seven gestational time periods than as a whole. Please note that although the model was sufficiently powered to test the hypotheses, given the small effect sizes found here for individual predictors (which are consistent with the literature), the model is not sufficiently powered to find significance in theIn this phase of the data analysis, thirty specific models were tested and compared. The first model comparison was between the full hypothesized model represented by Figure 4.20 and the null model shown in Figure 4.21, in which all of the predictors were restricted, specifying that there was not a relationship between gestational length and varying levels of the predictors during seven gestational time periods.

No less than in the evaluation of birthweight in the previous section, upon initial consideration of *Latent Social Support Model*, the latent social support variable did not make sense. For reasons already described above, the decision was made to split the latent social support construct into its' component manifest variables and use those as direct predictors of gestational length in the model. This model, known as the *Split Social Support Model*, was also significantly different from its' null. Unlike in the case of birthweight, in *Latent Social Support Model* for gestational length, although the -2LL is lower in the constrained model, the AIC is lowest for the restricted model, whereas in the *Split Social Support Model*, the AIC and the -2LL and are both lower for the unrestrained model(see Table 4.15). Given that the AIC is a relative measure of fit that considers both the goodness of fit and the complexity of the model, it is not surprising that an AIC would be lower for a simpler model. It is interesting to note though that in this constrained *Latent Social Support Model* the only significant predictor is maternal age. For every 4 years and six months younger the woman is, there is an average increase in mean gestation of 15 days.

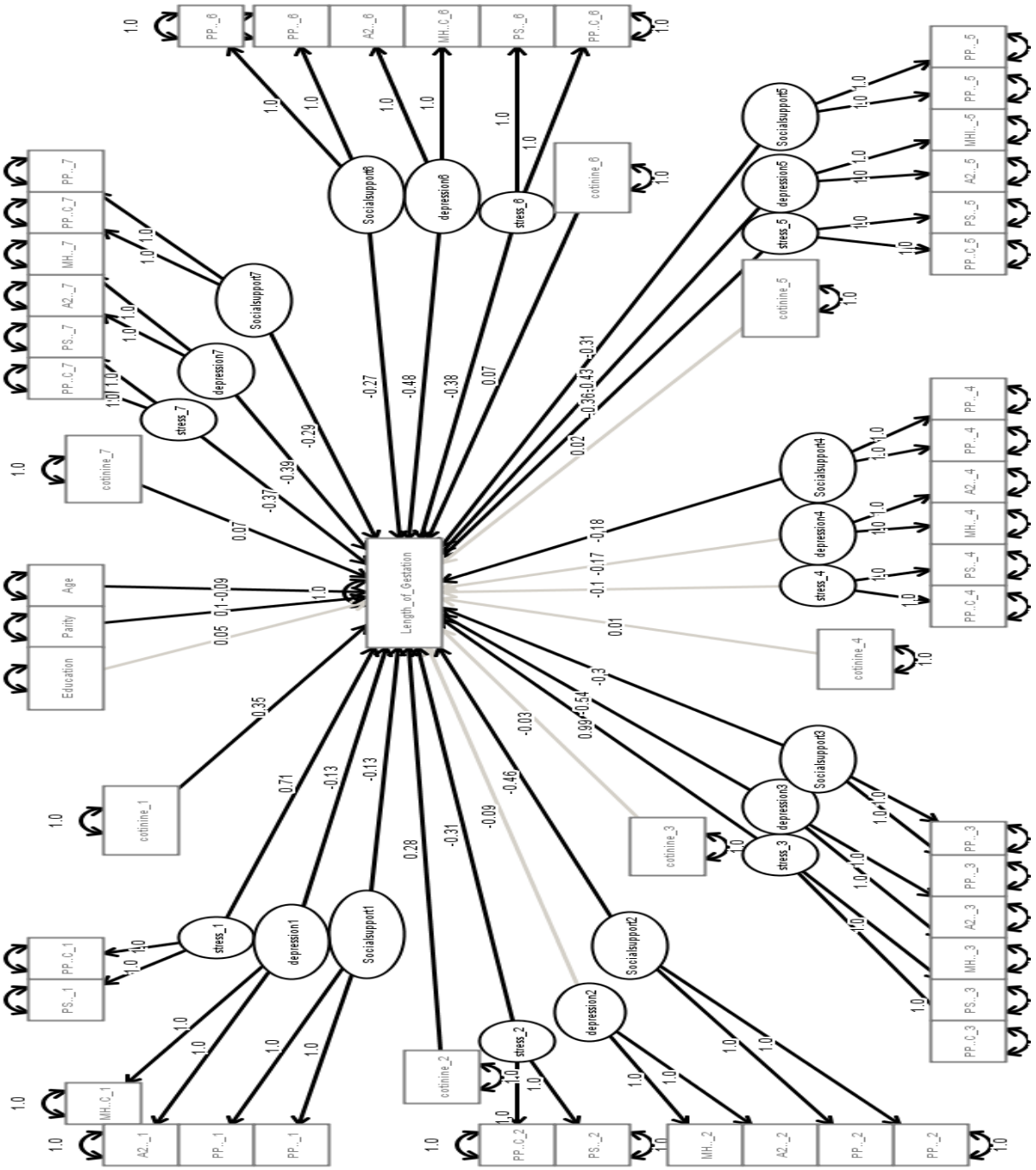

Figure 4.20. The *Latent Social Support Model* for Gestational Length. The latent constructs load to manifest variables from all time periods, and the manifest cotinine values are comprised of responses from the entire gestational period. Significant paths are in black ($p<0.01$), non-significant path is in gray. The latent constructs appear in black and the manifest variables are in gray.

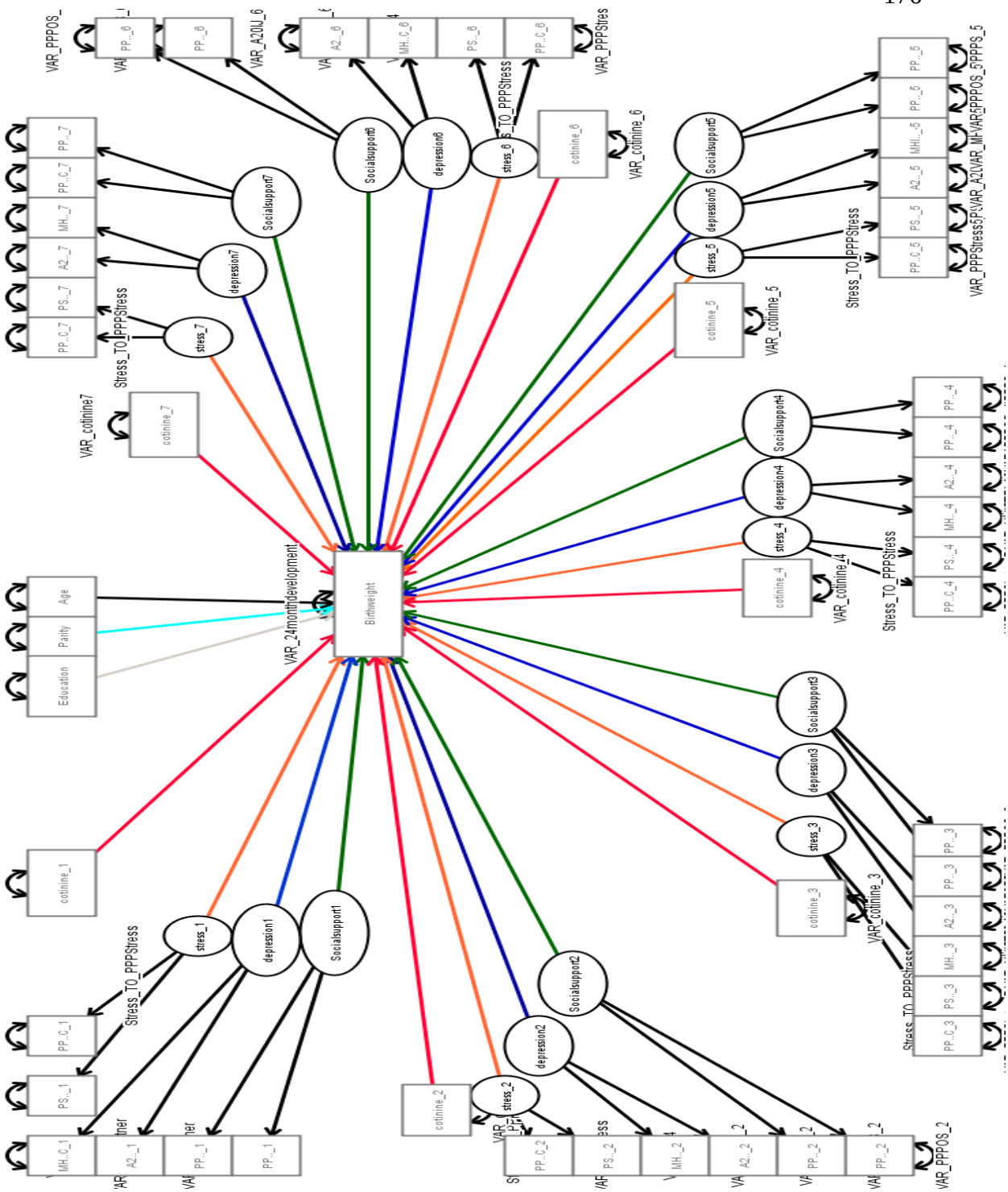

Figure 4.21. The *Latent Social Support Model* Null for Gestational Length. The latent constructs load to manifest variables from all time periods, and the manifest cotinine values are comprised of responses from the entire gestational period. All paths are significant ($p<0.01$). The latent constructs appear in black and the manifest variables are in gray.

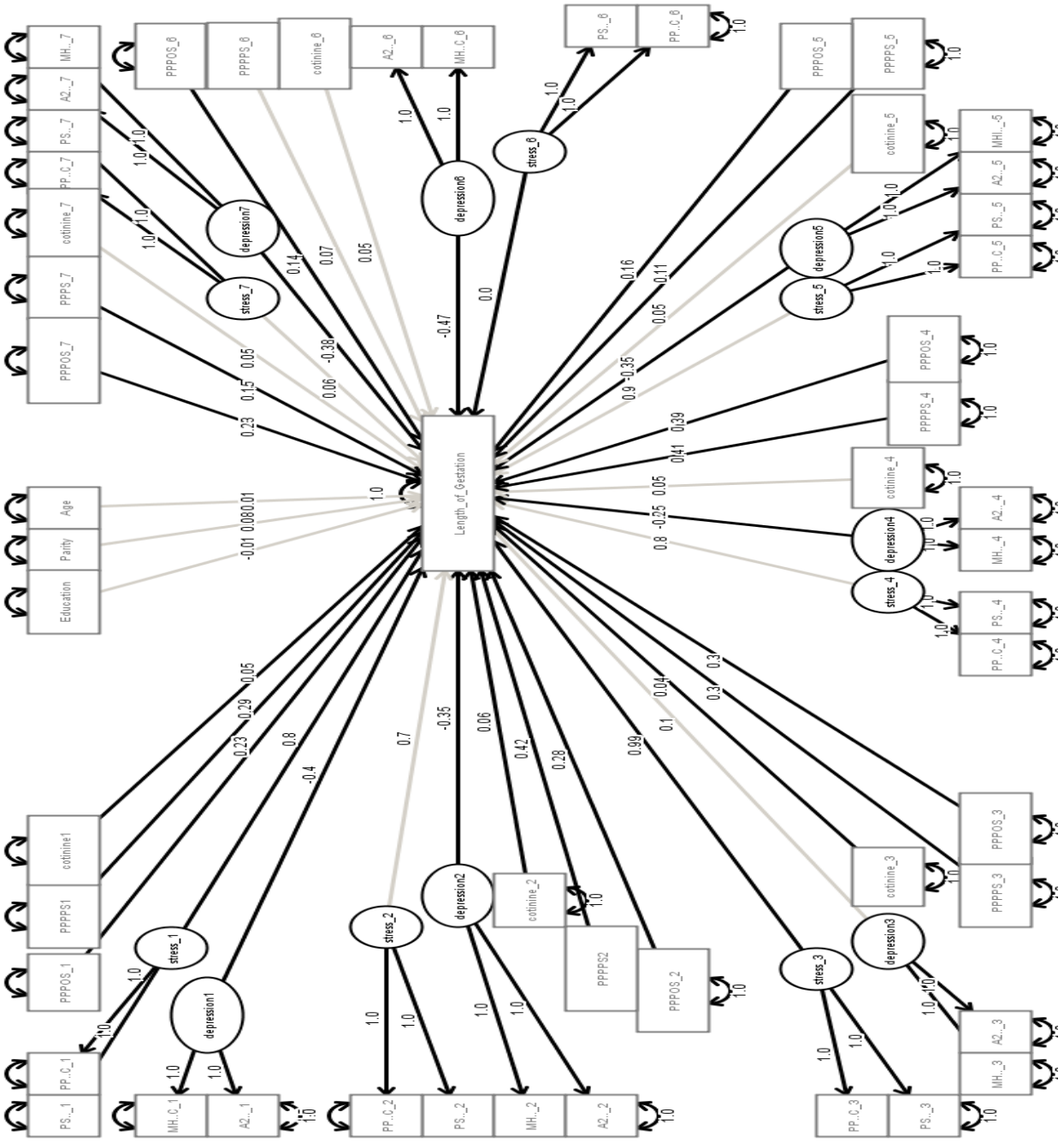

Figure 4.22. Social Support Split model for Gestational length with pathweights. Significant (at least $p<0.05$) path arrows are in black; gray arrows were not found to be significant in this model Latent constructs are in black and manifest variables are in gray. Variances show their starting values, not the model estimates. All variances were significant. *From :Gestational length Split Social Support Model.12_27_13.xml*

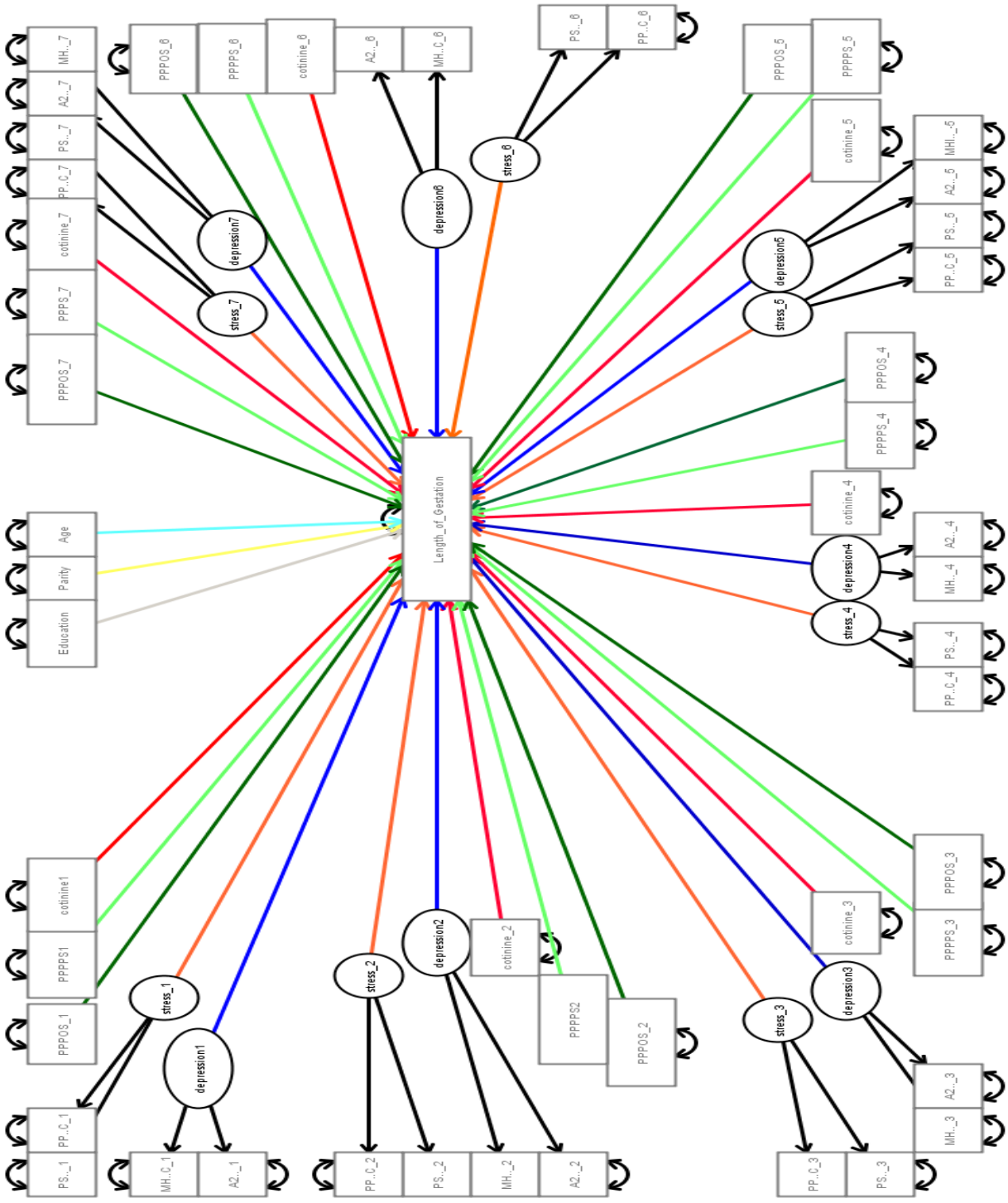

Figure 4.23.Social Support Split Null Model for Gestational Length. The latent constructs load to manifest variables from all time periods, and two social support paths and cotinine path are comprised of responses from the entire gestational period. Significant paths are in black ($p<0.01$), non-significant path is in gray. The latent constructs appear in black and the manifest variables are in gray.

There is sufficient evidence based upon the *Latent Social Support Model* comparison in Table 4.15 with its fully restricted counterpart to warrant rejection of the claim that variation in levels of stress, depression and social support, does not impact gestational length. Variations in gestational length are better explained by examining the predictor variables separately during seven gestational time periods than as a whole. Both the *Latent Social Support Model* and the *Split Social Support Model* establish that timing of these predictors during pregnancy matters in regard to gestational length.

Although the optimality conditions were satisfied for these models, meaning that an optimal solution was found, the comparison of each of the full models (*Latent Social Support Model* and the *Split Social Support Model)* with their restricted counterparts found significance without converging.

Regression Weights for Gestational Length.

Standardized Path Comparisons.

There is a full explanation of the different type of path estimates discussed at the beginning of the corresponding section on standardized path comparisons for the birthweight model. The individual variable path estimates loading to birthweight will be examined for the *Split Social Support Model* since it has the better fit indices and theoretically the data correlations make more sense. The *Latent Social Support Model* comparison of standardized estimates is presented in Figure (4.24) to allow the reader to judge the similarities and divergence between this originally theorized model and the *Split Social Support Model* (Figure 4.25) and the *Latent Social Support Model.* When social support is split into two types of support the intercepts and "slope" across time are

tempered and remain closer to the mean across groups. It is the predictors from the *Split Social Support Model* that will be examined individually in the following sections. The path estimates are listed in Table 4.16.

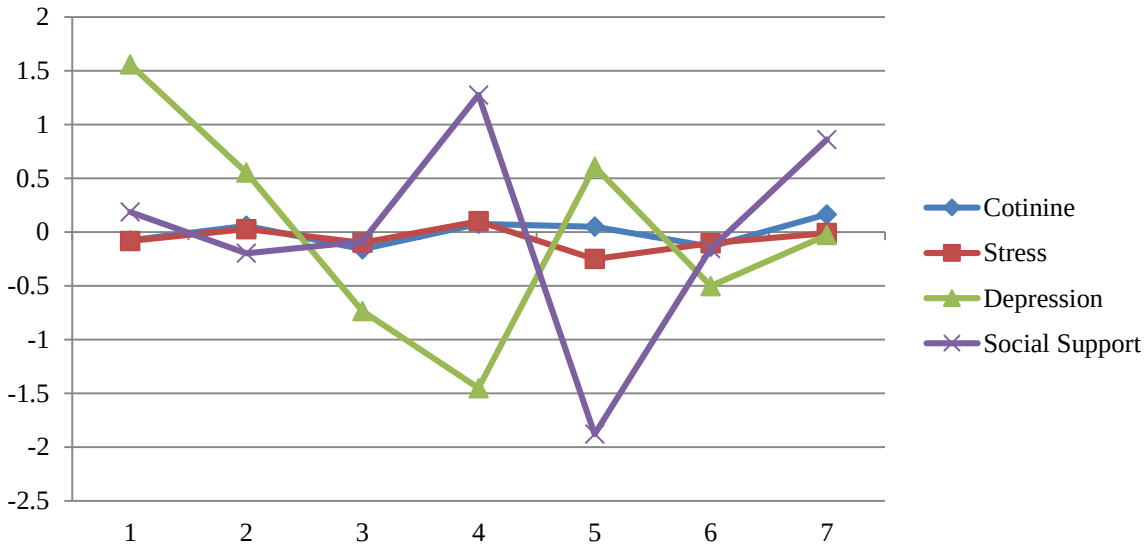

Figure 4.24. Standardized Comparison of Estimates from the *Latent Social Support Model* for loadings to Gestational Length across Groups

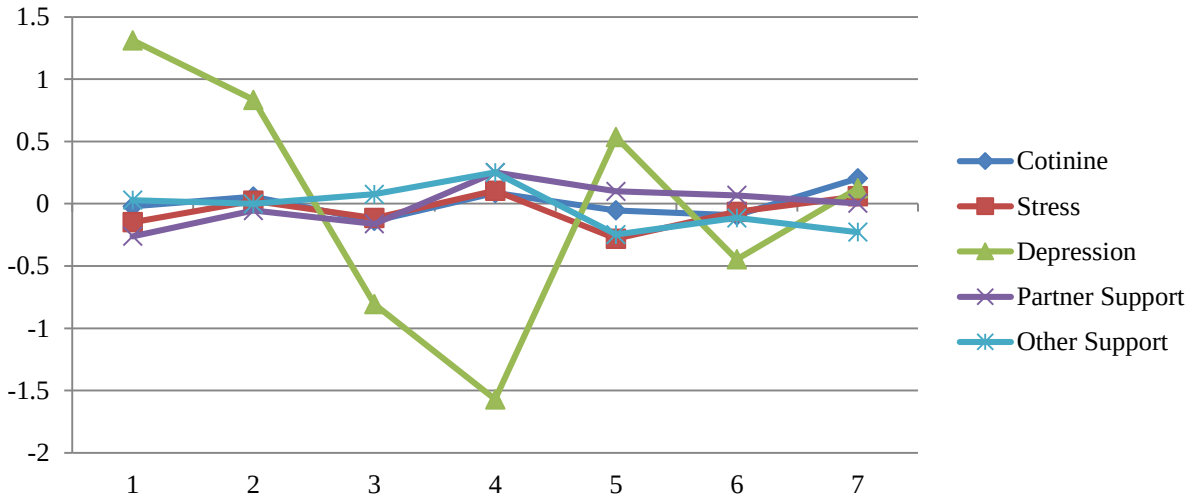

Figure 4.25. Standardized Comparison of Estimates from the *Split Social Support Model* for loadings to Gestational Length across Groups

The interpretation of the following standardized estimates assumes that any prediction of the dependent variable by the independent variable occurs while controlling for all other variables in the model.

Cotinine Path Estimates

The path weights for cotinine are graphically depicted in Figure 4.26 and listed in Table 4.16. These path weights are not statistically significant at any time point. Both groups 3 and 7 approach but do not reach statistical significance with p values of 0.07 and 0.08 respectively.

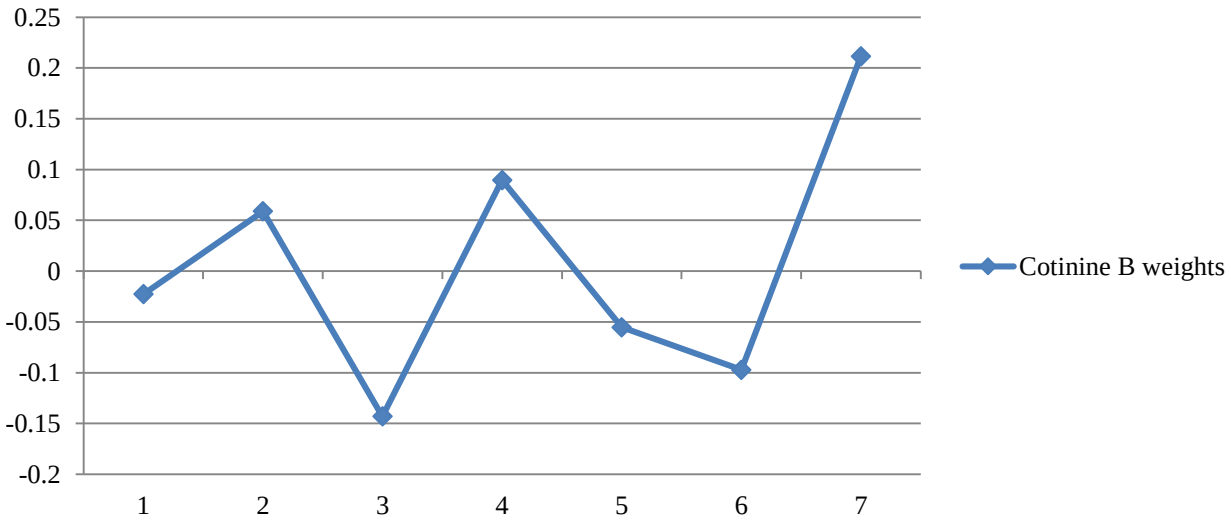

Figure 4.26. Unstandardized Cotinine Estimates from the *Split Social Support Model* for loadings to Gestational Length across Groups

Table 4.16

Unstandardized and Standardized Path Estimates for Gestational Length in the Unrestricted Split Social Support Model

Predictor	Regression Weight	Standard Error	Standardized Beta Weight	Standardized Standard Error	t- statistic
Cotinine_G1	-0.022657	0.170643	-0.021853	0.164586	-0.13
Cotinine_G2	0.058882	0.073876	0.056792	0.071253	0.79
Cotinine_G3	-0.142986	0.078769	-0.137911	0.075973	-1.81
Cotinine_G4	0.089656	0.095733	0.086474	0.092334	0.93
Cotinine_G5	-0.055229	0.135164	-0.053269	0.130366	-0.40
Cotinine_G6	-0.097270	0.113586	-0.093817	0.109554	-0.85
Cotinine_G7	0.211329	0.122815	0.203828	0.118455	1.72
Stress1	-0.244821	0.276939	-0.148158	0.167595	-0.88
Stress2	0.037228	0.13076	0.023635	0.083016	0.28
Stress3	-0.190822	0.164113	-0.114996	0.098899	-1.16
Stress4	0.189453	0.243106	0.104370	0.133927	0.77
Stress5	**-0.441556**	**0.21239**	**-0.281169**	**0.135243**	**-2.07***
Stress6	-0.100350	0.136092	-0.065120	0.088314	-0.73
Stress7	0.091367	0.235758	0.059549	0.153658	0.38
Depression1	0.167620	0.116039	1.312044	0.908293	1.44
Depression2	0.106468	0.092754	0.834518	0.727025	1.14
Depression3	-0.102880	0.063971	0.806502	0.501479	-1.60
Depression4	-0.200722	0.133762	-1.570535	1.046610	-1.50
Depression5	0.068024	0.129987	0.534317	1.021016	0.52
Depression6	-0.056786	0.056877	0.446557	0.447269	-0.99
Depression7	0.015466	0.068697	0.123895	0.550314	0.22
Partnersupport1	**-0.271091**	**0.126482**	**-0.261469**	**0.121992**	**-2.14***
Partnersupport2	-0.057136	0.067783	-0.055108	0.065376	-0.84
Partnersupport3	**-0.166724**	**0.084515**	**-0.160806**	**0.081514**	**-1.97***
Partnersupport4	**0.260332**	**0.090882**	**0.251092**	**0.087657**	**2.86****
Partnersupport5	0.102752	0.127256	0.099105	0.122738	0.80
Partnersupport6	0.070125	0.0793	0.067636	0.076485	0.88
Partnersupport7	0.002512	0.127233	0.002423	0.122717	0.01
Othersupport1	0.029518	0.136894	0.028470	0.132035	0.21
Othersupport2	-0.000725	0.06718	-0.000699	0.064795	-0.01
Othersupport3	0.079556	0.076322	0.076732	0.073613	1.04
Othersupport4	**0.260331**	**0.090882**	**0.251091**	**0.087656**	**2.86****
Othersupport5	**-0.256580**	**0.107946**	**0.247473**	**0.104114**	**-2.37***
Othersupport6	-0.118313	0.067998	0.114113	0.065584	-1.73
Othersupport7	**-0.236566**	**0.106271**	**-0.228170**	**0.102499**	**-2.22***
Age	**-0.168487**	**0.040763**	**-0.162507**	**0.039315**	**-4.13****
Education	0.070334	0.040926	0.067837	0.039473	1.71
Parity	0.017108	0.039977	0.016500	0.038558	0.42

* $p < 0.05$
** $p < 0.01$

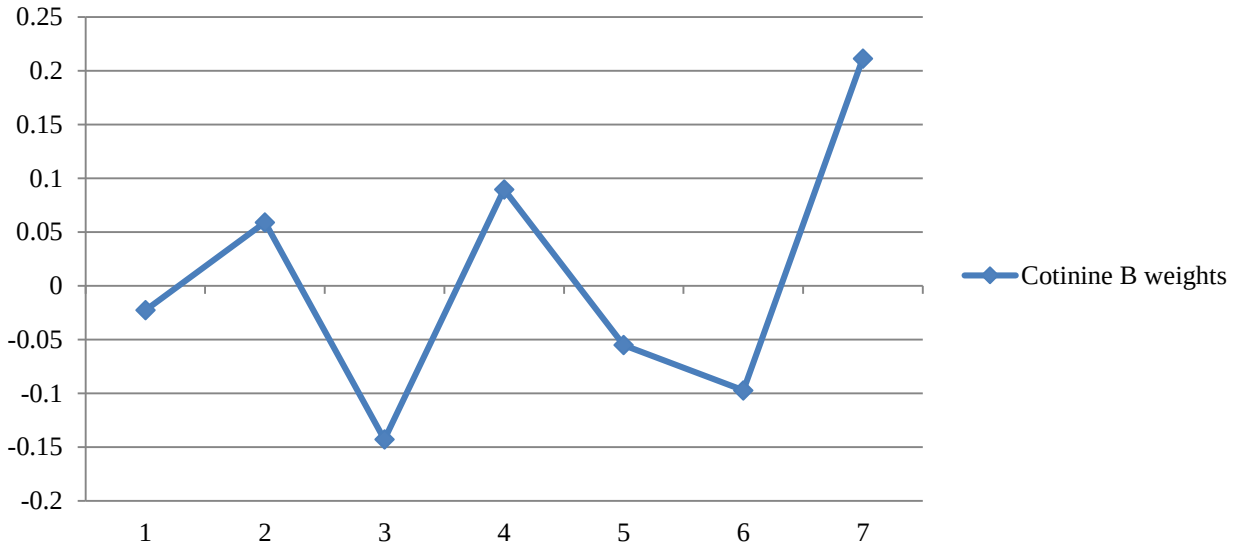

Figure 4.26. Unstandardized Cotinine Estimates from the *Split Social Support Model* for loadings to Gestational Length across Groups

Stress Path Estimates Loading to Length of Gestation

In the *Split Social Support Model* shown in Figure 4.27, the stress regression weights are only significant (p= 0.037) in Group 5 (24-28 weeks). During this stage of pregnancy, higher stress is associated with shorter gestations. For each increase of one unit in the latent construct of stress for Group 3, there is an average decrease in the mean gestation of about 2 days.

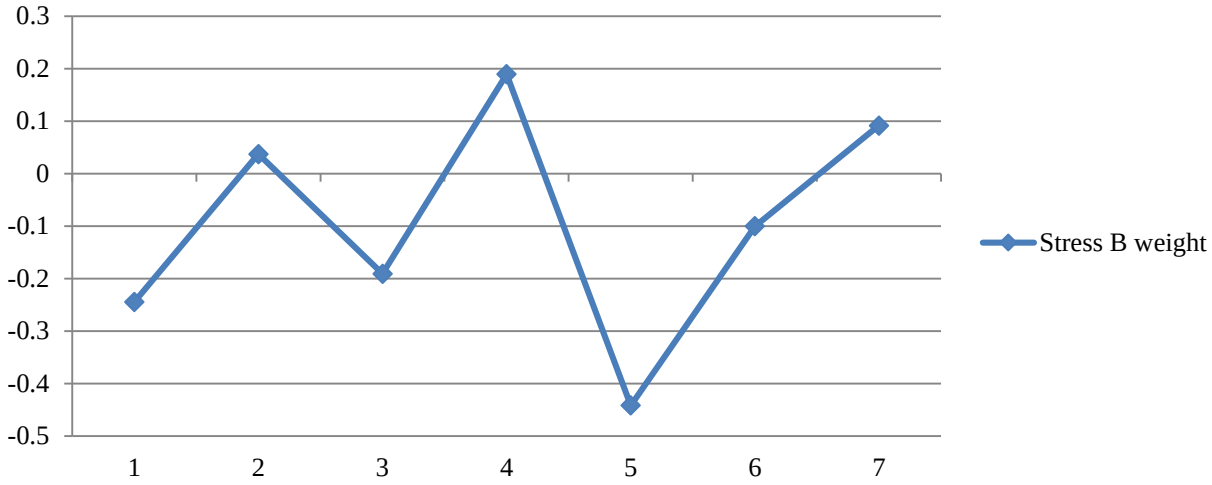

Figure 4.27. Unstandardized Stress Estimates from the *Split Social Support Model* for loadings to Gestational Length across Groups

Depression Path Estimates Loading to Gestational Age

The *Split Social Support Model* portrayed in Figure 4.28 did not return statistically significant path estimates for any groups. The path estimates for Groups 1,3 and 4 somewhat approached significance with p values of 0.1.

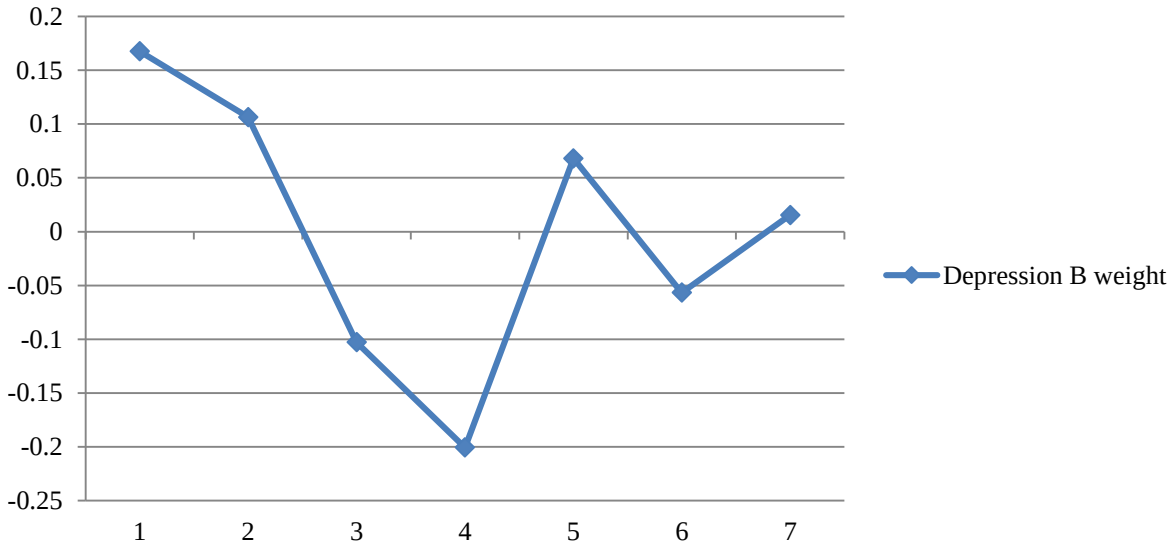

Figure 4.28. Unstandardized Depression Estimates from the Social Support Split Model for loadings to Gestational Length across Groups

Social Support Path Estimates for Length of Gestation

The *Split Social Support Model* evaluated the predictors of Partner Support and Other Support separately (see Figure 4.29 for comparison). Out of the 14 paths in these two scales, half of them were significant, demonstrating that social support is associated with gestational length.

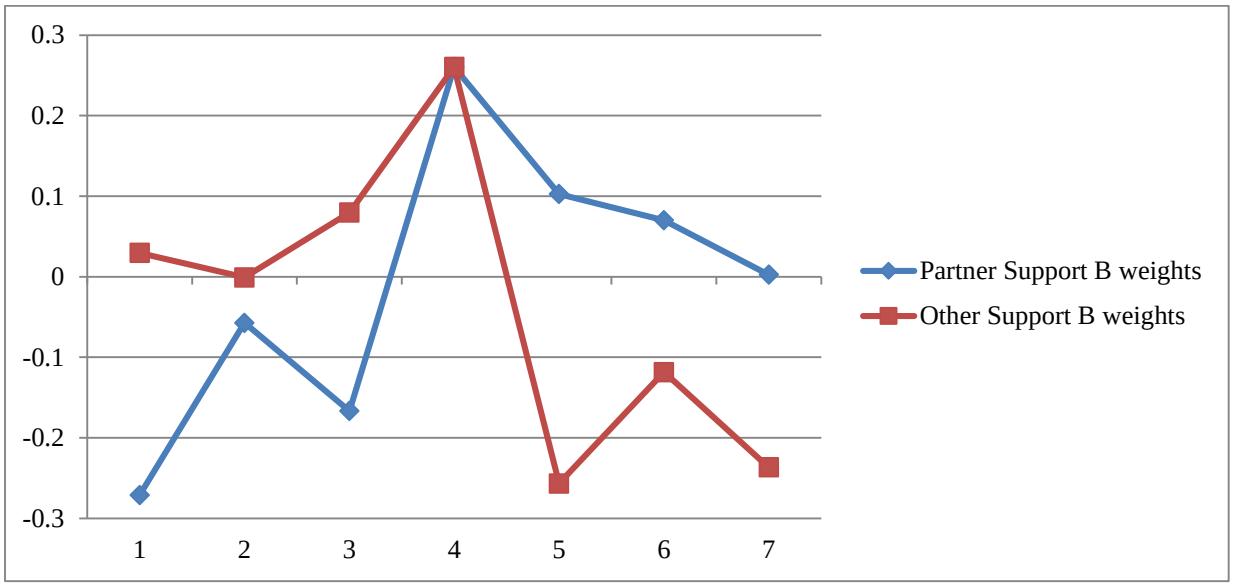

Figure 4.29 Comparison of Unstandardized Depression Estimates from the *Split Social Support Model* for loadings to Gestational Length across Groups. These can be compared directly; the instrument questions are the same on both scales.

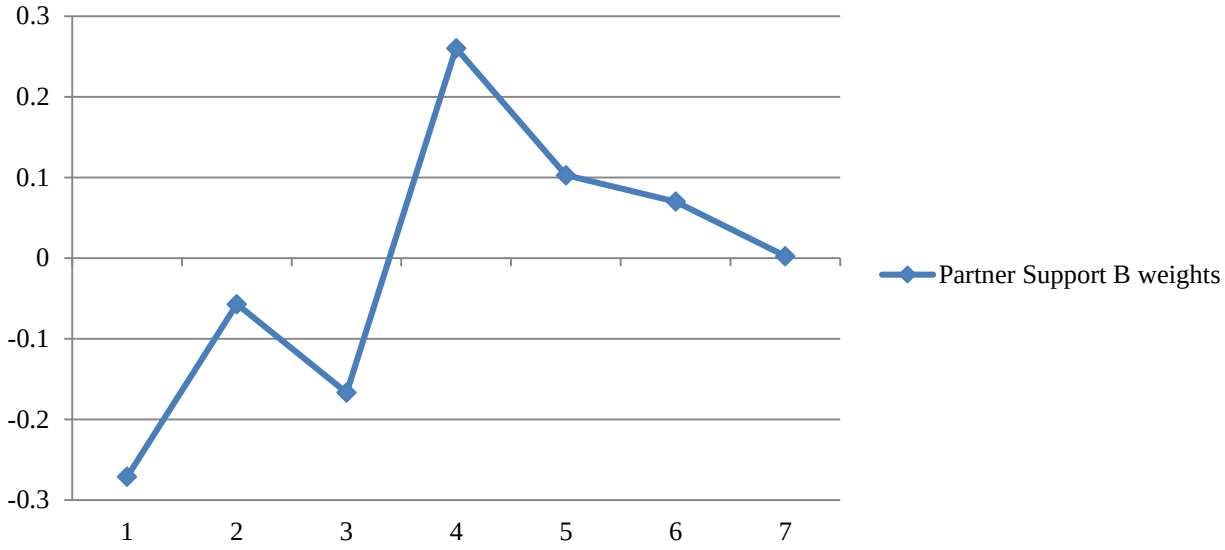

Figure 4.30. Unstandardized Partner Support Estimates from the Social Support Split Model for loadings to Gestational Length across Groups

On both of the support subscales, an 11 point difference in scale could represent either a one point change on the likert scale for each question, a complete reversal on 2 questions, from 1 or 6 to the other extreme, or any combination of changes in between. Examination of the Partner Support subscale regression weights (Figure 4.30 and Table 4.16) reveals significant paths for Groups 1, 3 and 4. For women in Group 1, for every 17.28 points increase in the PPP Partner Support subscale there is an average decrease in mean gestation of 4 days. An increase in 22 points in Group 3 was associated with an average decrease in mean gestation of 3 days. In Group 4, an increase in 21 points on the PPP Partner subscale was associated with an average increase in mean gestation of 4 days.

The Other Support regression weights were significant for Groups 4, 5, and 7 (Figure 4.32). Group 6 approached significance with a p-value of 0.08. A 13 point increase in the PPP Other Support subscale for Groups 4 was associated with an average

mean increase in gestation of 4 days, while in Group 5 the same increase in points was associated with an average mean decrease in gestation of 4 days. An increase of 15 points at Group 7 had essentially equal impact, a decrease in gestation of 4 days.

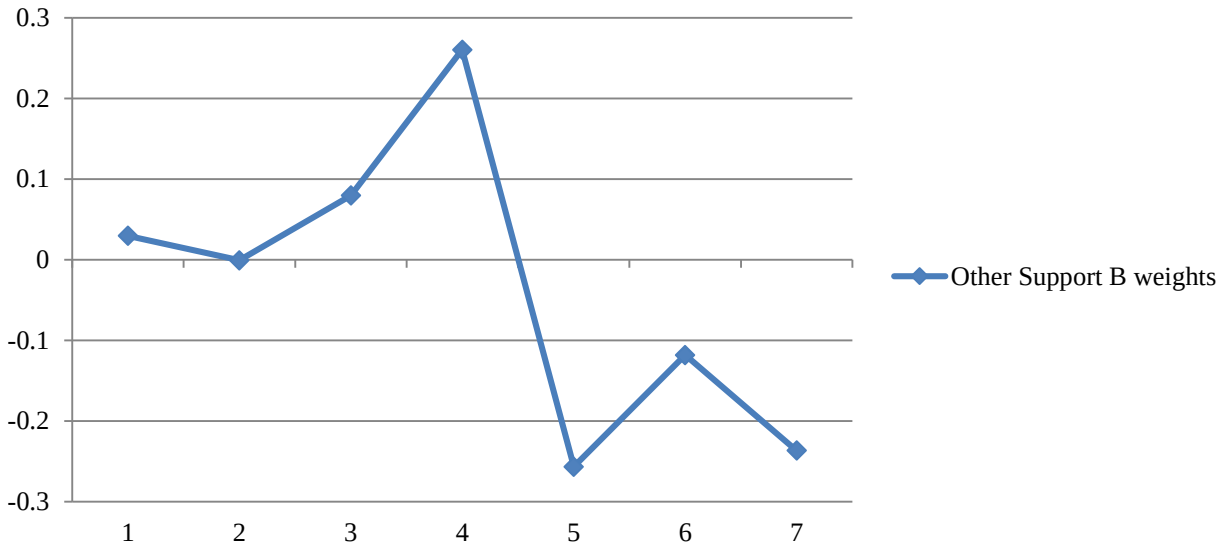

Figure 4.32. Unstandardized Other Support Estimates from the Social Support Split Model for loadings to Gestational Length across Groups

Summary of Hypothesis 1

Based on the significance testing of the standardized effects, the option of deleting the non-significant and/or smallest effects found in the full Social Support Split Model is considered for both birthweight and gestational length. However, model trimming driven by empirical criteria of statistical significance actually cause Type II error (Kline, 1998). The paths that are not significant in this model may apply only to the particular women in the BabyBEEP study. In addition, there is concern that although the model was powered to answer the hypothesis, that there is a difference in impact of cotinine use, stress, depression, and social support on birthweight and length of gestation based on time during pregnancy, the model was not powered sufficiently to ensure that

all significant paths would be found with an 80 percent probability. Therefore, the social support split model was retained and evaluated.

Evaluating two dependent variables separately with the same independent variables, provides an opportunity to compare the estimates from both the birthweight and gestational length models with each other. A comparison of each models' significant effects is presented in Table 4.17.

Table 4.17

Comparison of Significant Effects from Birthweight and Gestational Length Models

Predictor	Birthweight Beta Weights	Gestational Length Beta Weights
Cotinine 1		
Cotinine 2		
Cotinine 3		
Cotinine4		
Cotinine5		
Cotinine6		
Cotinine7		
Stress1		
Stress2		
Stress3		
Stress4		
Stress5	-0.2640328	-0.2811696
Stress6	0.2106948	
Stress7		
Depression1		
Depression2		
Depression3		
Depression4		
Depression5		
Depression6		
Depression7		
Partnersupport1		-0.2614698
Partnersupport2		
Partnersupport3		-0.1608065
Partnersupport4		0.2510916
Partnersupport5		
Partnersupport6	0.1815110	
Partnersupport7		
Othersupport1		
Othersupport2		
Othersupport3		
Othersupport4		0.2510916
Othersupport5	-0.2305381	-0.2474735
Othersupport6	-0.1634522	
Othersupport7	-0.1910085	-0.2281700
Age		-0.1625071

Note. Based upon the Social Support Split Model regression weights. Beta weights are standardized and thus can be compared among all variables. Negative beta weights indicate an inverse relationship between the predictor and the outcome variable. Positive beta weights indicate a positive relationship between the predictor and the outcome variable.*updated 1/11/14(based on dataset BB.H1.FINAL.stand.1_11_14)*

Hypothesis 2

The final model evaluation conducted using SEM with OpenMX(Boker et al., 2012) tested the hypothesis that there are differences in timing of predictors impact on the dependent variables of gestational length and birthweight according to whether or not women are experiencing perinatal intimate partner violence (IPV). As in the model testing for the first hypothesis, the missing data that was present due to the restructuring of groups from the original BabyBEEP dataset was managed using full information maximum likelihood procedures. Model fit was evaluated using minus 2 log likelihood (-2LL) and Akaike Information Criterion (AIC). For each latent variable, model identification was established by fixing the loading of the indicators at 1.0. If a latent variable loaded to a manifest variable, then the variance was freely estimated for that manifest variable. If the predictor had a direct path to the outcome variable the variance was fixed at 1.0.

The model comparison for this question involved splitting the BabyBEEP dataset into two groups, women who were abused and not abused. In the restricted model evaluation, the constraint of equality was placed upon the two groups, abused and not abused; their parameters or path weights were evaluated as equal in both groups. In the full unrestricted model, all parameters were left as separate, or potentially unequal. The constraints placed on the restricted model increased the degrees of freedom by 83.

Essentially, whether or not the fit of the restricted and full models is significantly different is determined through calculation of the difference in their two chi-squares and testing the likelihood ratio against a chi-square distribution with 53 degrees of freedom. For both birthweight and gestational length, the chi-squares were found to be significantly different (Table 4.18). The determination was made by running the model for IPV+ women, and for IPV – women, and combining their two minus two log likelihoods in order to obtain a minus 2 log likelihood estimate the *IPV Unique Paths Model.* Therefore there was sufficient evidence to warrant rejection of the claim that there are no differences in timing of risk factor impact on outcome between women who are abused and women who are not abused.

Table 4.18
Calculation of Significance of difference between IPV positive and IPV negative women in the BabyBEEP dataset

	Birthweight	Gestational Age
-2ll Split Social Support Model	31881.08	31935.98
-2ll IPV +	10588.61	10582.56
-2ll IPV-	20495.64	20551.13
-2ll IPV Unique Paths Model	31084.25	31133.69
LR	796.83	802.29
p	1.208E-133	9.3767E-135

Note. In the restricted model the path estimates are fixed to be the same for both IPV positive and IPV negative women, in the IPV Unique Paths Model the path estimates are allowed to be different. df=53 The shaded areas represent the -2ll that are combined to achieve the -2ll for the IPV Unique Paths Model.

The comparison that follows is solely of the significant path estimates that were found in the evaluation of the separate modeling of IPV positive and IPV negative women (see Table 4.19). As previously noted, the model was not powered to find significance in these paths, so lack of significance should not be interpreted as confirmation of the null hypothesis. The interpretation of the following standardized

estimates assumes that any prediction of the dependent variable by the independent variable occurs while controlling for all other variables in the model.

Table 4.19

Comparison of Significant Effects from Birthweight and Gestational Length Models Split by Perinatal IPV experience.

	Perinatal IPV -		Perinatal IPV +	
Predictor	Birthweight Beta Weights	Gestational Length Beta Weights	Birthweight Beta Weights	Gestational Length Beta Weights
Cotinine 1				
Cotinine 2				
Cotinine 3				
Cotinine4				
Cotinine5				
Cotinine6				0.339191118
Cotinine7				
Stress1				
Stress2				
Stress3				-0.431612442
Stress4				
Stress5	-0.431419011			
Stress6	0.257391857			
Stress7				
Depression1			-1.807095139	
Depression2				
Depression3				
Depression4			-0.933285712	
Depression5				-0.514939933
Depression6				
Depression7				
Partnersupport1				
Partnersupport2		-0.288116934		-0.464022922
Partnersupport3				
Partnersupport4				
Partnersupport5				
Partnersupport6		0.310416938		
Partnersupport7	0.217471363			
Othersupport1				
Othersupport2				
Othersupport3				
Othersupport4				
Othersupport5				0.288069898
Othersupport6	-0.256762802			
Othersupport7				
Age		-0.130583367		-0.18127090

Note. Based upon the *IPV Unique Paths Model* regression weights. Beta weights are standardized and thus can be compared among all variables. Negative beta weights indicate an inverse relationship between the predictor and the outcome variable. Positive beta weights indicate a positive relationship between the predictor and the outcome variable. *updated 1/11/14(based on dataset BB.H1.FINAL.stand.abuse.1_11_14)*

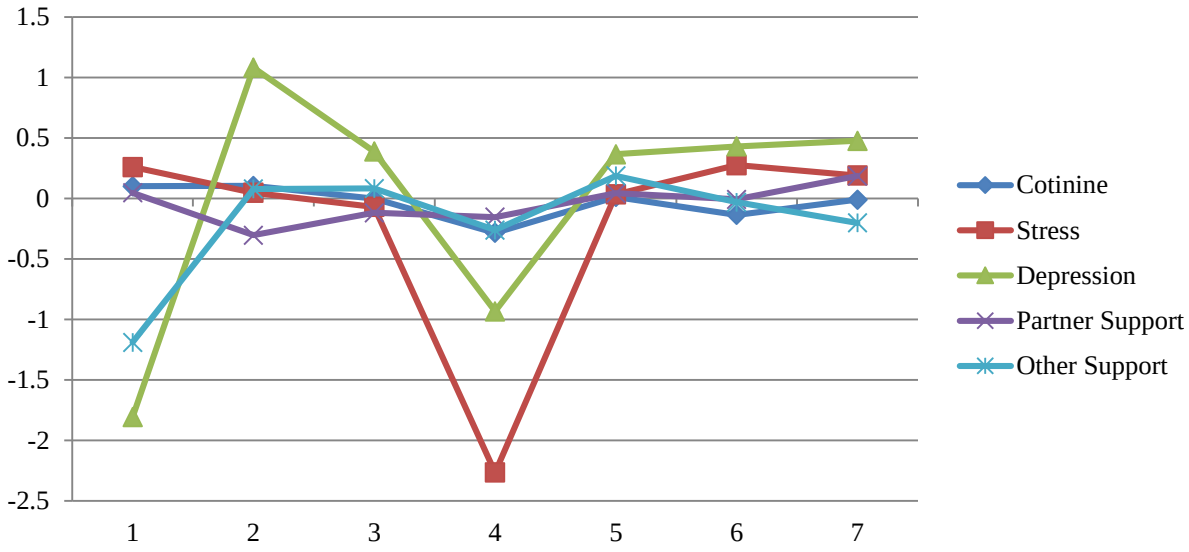

Figure 4.33. Standardized predictor loadings from the *IPV Unique Paths Model* for IPV positive women only loadings to Birthweight across Groups. Only Depression at Group 1 and Group 4 are significant regression weights.

Comparison of significant path estimates for birthweight between IPV Positive and IPV negative women.

There were only 2 significant beta weights in the birthweight model for abused women. In group 1 (4-9 weeks) for each one unit increase in the latent construct of depression in IPV positive women there was an average decrease in birthweight of 992 grams. Additionally, in group 4 (19-23 weeks) a one unit increase in the latent construct of depression in this same cohort of women was associated with an average decrease in birthweight of 512 grams.

In contrast, in the IPV negative group (see Figure 4.34), which had a larger sample size, thus more power; there were 4 significant regression weights. As it was in the evaluation of the

Split Social Support Model for the entire BabyBEEP population, for IPV negative women, Stress is significant in group 5 and group 6, with opposite effect. For every unit increase in the latent construct of stress in group 5 (24-28 weeks) there is an average decrease in birthweight of 235 grams. In group 6 (29-31 weeks), stress has the opposite effect; a one unit increase in the latent construct of stress was associated with an average increase in birthweight of 140 grams.

The IPV negative group also had significant path weights for Other Support in group 6 (29-31 weeks) and Partner Support in group 7(32-37 weeks). For every 11 point increase on the PPP Other Support subscale, there was an average decrease in birthweight of 140 grams. But an increase of 22 points on the PPP Partner Support subscale yielded an average increase in birthweight of 119 grams in group 7.

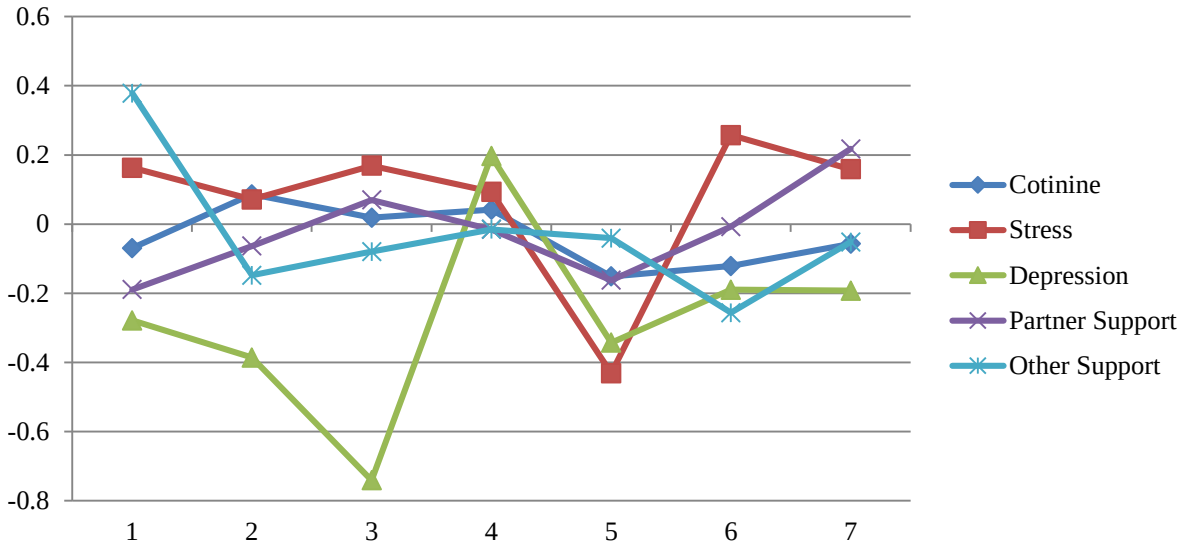

Figure 4.34. Standardized predictor loadings from the *IPV Unique Paths Model* for IPV negative women only loadings to Birthweight across Groups. Only Stress at Groups 5 & 6, Partner Support at Group 7and Other Support at Group 7 produced significant regression weights.

Comparison of significant path estimates for length of gestation between IPV Positive and IPV negative women.

While there were only 2 significant paths in the model of abused women for birthweight, there are 5 significant paths in the model for gestational length. Interestingly, the birthweight model had 4 significant paths for the non-abused women, but the gestational length model has just 2 path estimates that reach the level of statistical significance in this underpowered model.

In regard to length of gestation, the standardized predictors for IPV positive women can be found in Figure 3.35; the IPV negative women's predictors are in Figure 3.36.

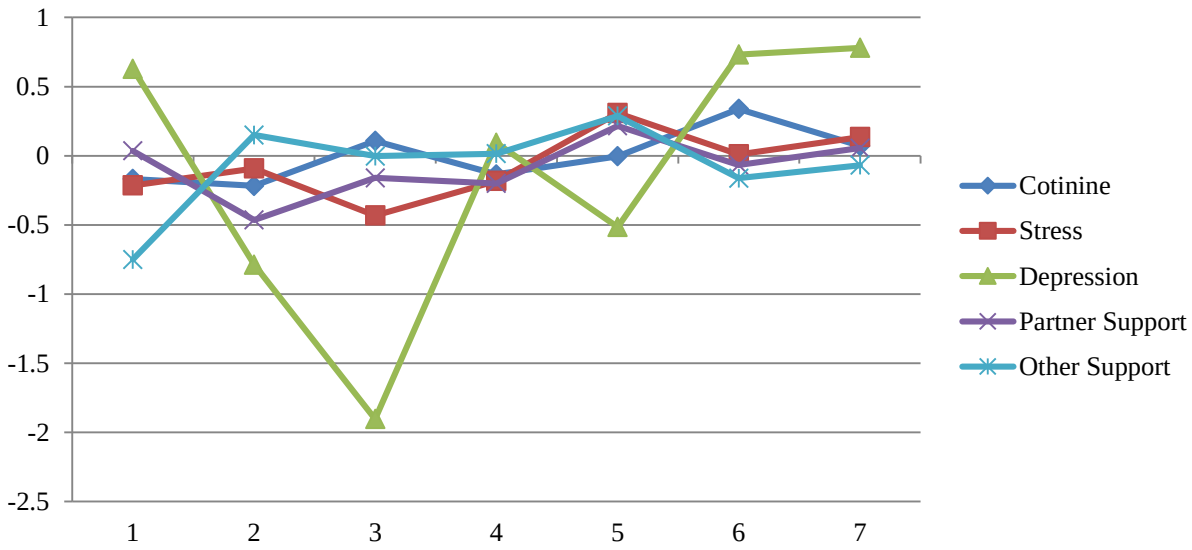

Figure 4.35. Standardized predictor loadings from the *IPV Unique Paths Model* for IPV positive women only loadings to Gestational Length across Groups. Significant regression weights include: Cotinine 6, Stress 3, Depression 5, Partner Support 5 and Other Support 5.

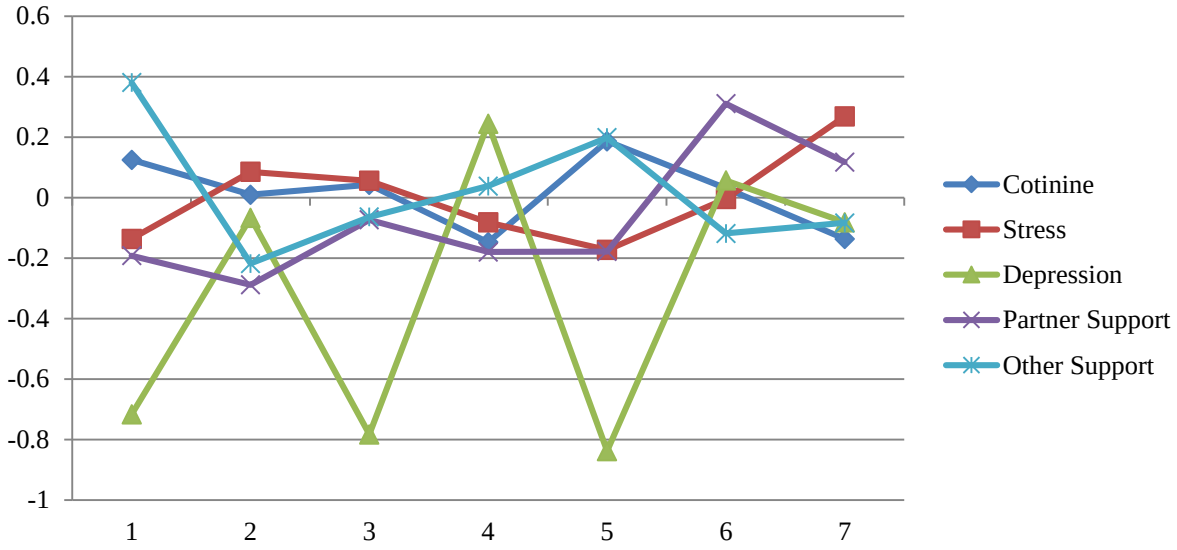

Figure 4.36. Standardized predictor loadings from the *IPV Unique Paths Model* for IPV negative women only loadings to Gestational Length across Groups. Only Partner Support at Group 2 and 6 are significant regression weights

In the *IPV Unique Paths Model* for IPV positive women there were several significant regression weights loading to length of gestation. Group 5 had two significant path estimates, for depression and for other support. An increase of one unit in the latent construct of depression was associated with an average mean decrease in gestation of 8 days. For IPV positive women in group 5 a 15 point increase on the PPP Other Support subscale was associated with an average mean increase in length of gestation of 5 days. As mean cotinine increased by 94 ng/ml in group 6 (29-31 weeks), the average length of gestation increased by 5 days. Stress was significant in group 3 (14-18 weeks), a one unit increase in the latent construct of stress resulted in an average decrease in gestation of 1 week. Finally, a mean increase in the PPP Partner support subscale of 23 points in group 2 (10-13 weeks) resulted in an average decrease in gestational length of 1 week.

The IPV negative women's model did not return as many significant path weights for gestational length, in spite of the increased sample size compared to the IPV positive

group. The only significant paths were for Partner Support. In early pregnancy, in group 2 (10-13 weeks) an increase of 18 points on PPP Partner support subscale resulted in an average decrease in mean gestational length of 4 days. Later, in group 6, an increase in the PPP Partner support subscale of 21 points was associated with an average increase in mean gestational length of 5 days.

Summary of Findings

The goal of this secondary data analysis was to evaluate the theory of AR using the data from the BabyBEEP study (R01NR05313) by examining the relationships between stress, depression, social support, intimate partner violence, birthweight and length of gestation. Overall, the study affirmatively answers the research question of whether different levels of stress, depression and social support at any particular month of gestation was more highly associated with birthweight or length of gestation after controlling for tobacco use (in a population of pregnant smokers). Two hypotheses were advanced at the outset. The central hypothesis was confirmed; the impact of stress, depression, tobacco use and social support on adverse birth outcomes does vary across the gestation. The second hypothesis, that intimate partner violence (IPV) during the perinatal period (during pregnancy or the year prior) would change the timing of the impact of other stress, mood and social support on birth outcomes was also confirmed. It was apparent in the means plots that a difference between the IPV positive and IPV negative women's perceptions of stress, depression, and cotinine levels is one of amplitude. On average the abused women were more depressed, perceived more stress and less social support than their non-abused counterparts. And although in group 1 the

IPV positive women used less tobacco, this was only true for group 1 and group 3; at all other time points they were smoking more than their IPV negative counterparts.

In the SEM that confirmed the central hypothesis there were several significant direct effects were found. The most significant effects were seen between 24 to 28 weeks gestation. For this group, increased stress, and paradoxically, increased social support from others was associated with a decrease in birthweight and length of gestation. More partner support prior to 18 weeks of pregnancy was also associated with shorter lengths of gestation. In this total sample, after 23 weeks social support from others demonstrated a negative association with birthweight and length of gestation. Partner support, on the other hand, was protective of birthweight between 29 and 31 weeks, but otherwise not a significant predictor of birthweight. And its negative effect on gestational length was only demonstrated prior to 23 weeks.

There was only one path direct effect that was shared when the sample was split into IPV positive and IPV negative women (see Table 4.20). This was the negative impact that partner support has on gestational length between 10 and 13 weeks of pregnancy; that is, the less partner support perceived by the woman, the longer the length of gestation. The negative impact of stress was significant earlier in pregnancies exposed to abuse (group 3 compared to group 5 in the IPV negative women). For the group not experiencing abuse, stress was actually protective of birthweight from 29-31 weeks gestation.

Regarding birthweight, the only significant predictor for the abused cohort was depression. Depression at 4-9 weeks gestation showed a very strong negative association

with birthweight in IPV positive women indicating that the less depressed a woman was in that group the more likely she was to have a heavier baby. This same cohort experienced another negative direct effect on birthweight between 19 and 23 weeks. Depression had a similar effect negative effect on length of gestation in the group immediately following, between 24 and 28 weeks, when more depression led to shorter pregnancies.

In the group of IPV negative women, partner support was protective of gestational length between 29 and 31 weeks, and of birthweight from 32 to 27 weeks gestation, while increased other support during that 29 to 31 week period was actually associated with a decrease in birthweight. In contrast, for the women experiencing perinatal IPV, other support from 24-28 weeks increased the length of gestations.

Also surprisingly, among this group of pregnant smokers, the women who smoked the most in group 6 (29-31 weeks gestation) were more likely to stay pregnant longer. Otherwise cotinine was not a significant predictor when the time points in pregnancy were assumed to be different. The significant association between higher salivary cotinine levels and longer gestations persisted through the 18th week of gestation. And the only significant direct effect linking increased cotinine use with lower birthweight was in the IPV positive group between 24 to 28 weeks of pregnancy.

Table 4.20

Comparison of Significant Effects from Birthweight and Gestational Length by Gestational Age Group

Group	Total	IPV-	IPV+
1	Partner Support GL		Depression BW
2		Partner Support GL	Partner Support GL
3	Partner Support GL		Stress GL
4	Other Support-GL Partner Support GL		Depression BW
5	Other Support-BW Other Support-GL Stress-BW Stress GL	Stress BW	Depression GL Other Support GL
6	Other Support-BW Partner Support BW Stress-BW	Other Support BW Partner Support GL Stress BW	Cotinine GL
7	Other Support-BW Other Support-GL	Partner Support BW	
	AGE-GL	AGE-GL	AGE-GL

Note: Positive direct effects are depicted in black and negative effects are in red, with shaded box.
BW=Birthweight
GL=Gestational Length

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Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this study was to test the theory of adaptive reproduction by examining the timing of the relationships between stress, depression and social support during pregnancy and the birth outcomes, birthweight and length of gestation in a population of smokers. This chapter presents a discussion of the findings. First the main findings from the exploration of linearity and Structural Equation Modeling (SEM) will be summarized. These will then be interpreted and placed within the context of relevant literature. The theoretical, methodological and clinical nursing implications for these findings will be discussed, as well as the limitations of the study. The chapter will conclude with a discussion of future research directions indicated by these findings.

The theory of Adaptive Reproduction (AR) presented in Chapter 2 posits that adverse birth outcomes, such as low birthweight (LBW) or preterm birth (PTB) are adaptive responses to environmental stimuli, and that social stresses or supports affect birthweight and gestational length. As the next section describes, this framework was supported by the research findings in this dissertation.

Summary

The goal of this secondary data analysis was to evaluate the theory of AR using the data from the BabyBEEP study (R01NR05313) by examining the relationships between stress, depression, social support, intimate partner violence, birthweight and length of gestation. Overall, the study affirmatively answers the research question of whether different levels of stress, depression and social support at any particular month of

gestation were more highly associated with birthweight or length of gestation after controlling for tobacco use (in a population of pregnant smokers). Two hypotheses were advanced at the outset. The central hypothesis was confirmed; the impact of stress, depression, tobacco use and social support on adverse birth outcomes does vary across the gestation. The second hypothesis, that intimate partner violence (IPV) during the perinatal period (during pregnancy or the year prior) would change the timing of the impact of other stress, mood and social support on birth outcomes was also confirmed. The means plots demonstrated that one difference between IPV positive and IPV negative women in this study is the amplitude of their perceived stress, depression and social support levels. On average, the abused women were more depressed, perceived more stress and less social support than their non-abused counterparts. And although they were generally not smoking as much as the IPV negative women in early pregnancy, as the pregnancy progressed (particularly after 19 weeks) IPV positive women's tobacco use was greater than that of IPV negative women.

This study supports and extends previous work on the impact of psychosocial stress on birth outcome and validates the AR theoretical framework. In the SEM that confirmed the central hypothesis, several significant direct effects were found that, together with the supported second hypothesis moves our understanding of the PNI of adverse birth outcomes forward.

There are five important findings in this study. The first important understanding derived from this study is that there is a difference in the timing of stress, depression, social support and cotinine use as predictors in women who are experiencing perinatal

IPV, compared to women who are not abused. The experience of violence changes the timing of the placental cell-signaling of the placenta which contributes to increased depression, lower birthweight and shortened gestations. A second important finding is that the strongest effects seen in the study were from stress at 24 to 28 weeks. Increased stress in this group of women led to lower birthweights and shorter lengths of gestation. Thirdly, depression was the most significant predictor of lower birthweight and shorter gestation in women experiencing perinatal IPV. Women who report more depression between 19 and 23 weeks have shorter gestations, and that report of increased depressive symptomology becomes a predictor of lower birthweight at the end of the second and beginning of the third trimester. The fourth important contribution of this study concerns the role of partner support. In women who are not abused, partner support is protective of birthweight and gestational length in the third trimester, but in women who are being abused, partner support during this time in gestation is not predictive. Moreover, for the IPV positive women, more partner support in the first trimester was associated with decreased lengths of gestation.

The fifth important understanding derived from this study concerns the role of social support from others at the end of pregnancy. Up until 24 weeks, social support from others is protective of gestational length, and for abused women this protection extends to the 28 week mark. However, in the third trimester, women with the least social support have the longest gestations. This is a particularly interesting finding in an AR context.

Interpreting and Contextualizing Findings

Adaptive reproduction suggests that adverse birth outcomes such as preterm birth and low birthweight are not pathological dysfunctions that occur due to inept or broken reproductive mechanisms, but rather these outcomes are adaptive physiologic responses to environmental causes that maximize a woman's overall evolutionary fitness and lifetime reproductive success.

IPV Findings

The second hypothesis in this study; whether the timing of psychosocial stress impact on birth outcomes is different for women experiencing perinatal IPV, can be viewed as a test of whether the psychoneurological and nuclear social-behavioral context induced by this particular environmental exposure (perinatal IPV) alters PNI signaling responses that occur during the normal physiologic processes of pregnancy, thus leading to the increased rate of adverse outcomes (Shah & Shah, 2010). The impact of perinatal IPV on psychosocial health has already been well-documented (Ansara & Hindin, 2011; Garrido, Culhane, Petrenko, & Taussig, 2011; Lindhorst & Beadnell, 2011). Recent work in IPV has demonstrated a significant relationship between IPV and maternal depression, distress, and infant LBW and PTB (Han & Stewart, 2014; Sanchez et al., 2013) and small for gestational age infants (Alhusen, Lucea, Bullock, & Sharps, 2013). Kiely et al. (2011) found that IPV was one of the most predictive determinants of poor birth outcomes. Compared to their non-abused counterparts in this study, women who experienced perinatal IPV were more likely to have other risk factors (specifically increased stress, depression, and tobacco use and lack of social support). And, according to this

dissertation work, when they experience these additional risk factors, it is in a more extreme form.

With respect to the issue of how perinatal IPV affects the timing of stress, depression, social support or cotinine impact on birthweight or gestational length, this study contributes an important finding: the impact of stress on gestational length occurs earlier in women who are experiencing abuse when compared to those who are not. This supports an adaptive reproductive PNI mechanism, rather than a biomedical one.

In the IPV positive population, there is an interesting positive association in the early third trimester, in which increased cotinine use is associated with increased birthweight. Tobacco use may be a coping mechanism that helps women cope with stress and/or depression. Cotinine use outside of pregnancy decreases the inflammatory response (Bagaitkar, Zeller, Renaud, & Scott, 2012); this finding supports the understanding that it can do this in pregnancy too, thus inhibiting the inflammatory cascade of the third trimester, and moderating the inflammatory effects of depression.

The psychological appraisal of violence directed at oneself by a partner appears to not only change the amplitude of the women's perceptions of stress, depressive symptoms or social support, but also to accelerate the timing of the relationship between the experience of stress and length of gestation. It also rescinds the protection afforded by any support the partner might be providing. Abused women perceive more stress, use more tobacco, have more depressive symptoms, and have less social support from their partner and from others than women who are not abused. Thus the environmental issue, perinatal IPV, becomes a psychoneurological issue, and the PNI processing of this

experience occurs in ways that likely accelerate the inflammatory cascade that occurs at the end of pregnancy, as well as changing the availability of nutrient resources for the fetus, leading to lower birthweights.

Stress Findings

The psychosocial risk associated with the latent construct of stress, comprised of perceived life stressors and perceived distress and anxiety, has received a great deal of attention in the literature, particularly in regard to its association with preterm birth.

Accelerated stress impact on length of gestation.

The neuroendocrine and neuroimmune processes that are activated by stress clearly do not cause an immediate outcome, as it is not the third trimester time points that are significant, even though this is when the majority of weight gain occurs in the fetus, and when the majority of births occur. Rather, the cell-signaling response to the perception of more stress in women who are experiencing perinatal IPV begins between 14 and 18 weeks of pregnancy, unfolds over weeks and months, contributing to a milieu that shortens gestational length and inhibits weight gain in the fetus. This is completely consistent with McLean et al's (1995) theory of setting the "placental clock". McLean's group intimated that second trimester CRH levels are directly attributable to the levels of perceived stress. McLean et al (1995) found that from 15 weeks EGA, women who exhibited higher levels of serum corticotropin releasing hormone (CRH) were more likely to deliver preterm. Wadhwa, Entringer, Buss, and Lu (2011), building on these findings, proposed that CRH is a major mediator in the relationship between stress and PTB. Since women who are experiencing abuse in the current study are the most stressed in this time

period, it is plausible that CRH is a mediator. Women who are not experiencing abuse are less stressed, and thus they may not share these early CRH spikes.

Clearly there are also processes initiated by the HPA axis response to stress in the late second trimester that alter the ability of the placenta to provide nutrients to the fetus. It remains to be seen whether this is directly connected to the processes that lead to higher serum levels of placental CRH in response to perceived stress. If this is what happens, then the presence of the elevated CRH that accelerates the inflammatory cascade, which usually occurs at the beginning of the third trimester, and reaches its peak about 20 days prior to delivery (McLean et al., 1995) may also blunt the exchange of nutrients, thus restricting fetal growth.

In women exposed to perinatal IPV, the stress impact on birth outcome occurs earlier than in the total sample or the IPV negative women alone. In addition to altered inflammatory activity, differences in stress reactivity throughout the course of pregnancy could affect this finding. Glynn et al. (2001) reported a blunting of stress responsivity as pregnancies progress. In their work on perceived stress after an earthquake, women in earlier pregnancy reported feeling more stressed than women in later pregnancy. As the pregnancy progressed, they describe a sort of regression to the mean, as the amplitude of perceived stress was blunted the closer the earthquake was to delivery. Their data was collected retrospectively; women were asked at 32 weeks gestation and again at 6 weeks postpartum, about how disturbing the earthquake had been. The results presented in this dissertation work represent prospectively collected longitudinal data that is not subject to the same recall biases.

Glynn's work (Glynn, Schetter, Hobel, & Sandman, 2008) examining women from 18-20 and 30-32 weeks, did not find a relationship between perceived stress and PTB; this is consistent with the finding in our study for these time points in the *Social Support Split* model . This current study extends their work, demonstrating that women exposed to perinatal IPV experience a point of stress impact on gestational length earlier in the pregnancy, between 15 to 18 weeks,. This study also supports their supposition that the later a stress occurs in pregnancy, the less likely it is to be related to preterm birth. Stress after 28 weeks gestation was not predictive of gestational length in one direction or the other.

However, increased stress between 24 and 28 weeks seemed to be protective, and for IPV negative women especially, had a positive effect on birthweight. These IPV negative women presumably did not have an acute environmental stress exposure similar to the violence being experienced by their abused counterparts. They can be viewed as having normal PNI stress resilience responses; their increased perception of stress between 24 and 28 weeks is helpful and actually promotes fetal growth. The IPV negative women in this study were likely able to mount a sympathetic nervous system response to the challenges in their environment. These routine intermittent responses to acute stresses may actually promote the typical placental signaling that is associated with healthy fetal weight gain. The ability to mount a usual response to acute stress is significantly compromised in people who are experiencing depressive symptoms (Southwick, Vythilingam, & Charney, 2005). And the IPV positive cohort was experiencing considerably more depression than the IPV negative group.

From 29 to 31 weeks, the women in the IPV negative group have a reversal of effect direction, related to stress and birthweight. Suddenly birthweight is no longer protected but is compromised by stress. This finding is in keeping with PNI models of stress adaptation. When initially dealing with a stress, the immune system is not in a depressed mode. But as the effects of stress accumulate, cortisol rises, and depression, which is an inflammatory condition, ensues (Leonard & Maes, 2012; Maes, 2011). It may be that the issues between stress and birthweight are mediated by similar pathways as those involved in the inflammatory response of depression.

Depression Findings

Whether or not depression contributes to shortened gestations has been a hotly debated issue in the literature for the past decade. In the constrained *Latent Social Support Model,* depression was a significant contributor to lower birthweights, which confirms the findings of a recent meta-analysis that depression is associated with both LBW and PTB (Grote et al., 2010) and through the evaluation of depression over seven months of pregnancy, extends current understanding of the relationship between depression, birthweight and gestational length. This is the first study to evaluate women ranging from 4 to 37 weeks, and it enhances the work of Dayan et al. (2002, 2006) and Jesse, Seaver, and Wallace (2003), disputing other work that there is no relationship between depression and gestational length.

This study also provides an extension to work by Elsenbruch et al. (2007) who claim that in women with low social support there is a negative association between depression and birthweight in the first trimester . In BabyBEEP women who were IPV

positive, depression from 4-9 weeks was associated with lower birthweights. Elsenbruch's group did not evaluate women prior to the 10th week or after the 13th week of gestation.

The depression construct in IPV positive women was the most highly correlated construct in the entire model and demonstrated that being more depressed is associated with both lower birthweights and lower gestational lengths. Birthweight is especially affected by both first and second trimester exposure, whereas length of gestation is not associated with depression until mid-pregnancy (24-28 weeks). Given the usual correlation between birthweight and length of gestation (the longer a fetus is in the womb, the more chance it has for weight gain); this suggests that depression is associated with preterm birth. This finding could be framed as a result of the increased activation of the HPA and immune systems in the presence of depression, and supports the understanding of depression mediating preterm birth in women experiencing IPV.

But this presupposes that depression causes the inflammation. It could be, in light of the bidirectional forces of PNI, that inflammatory processes underlie or even cause the symptoms of depression (Maes et al., 2012). It could be that the events that prematurely trigger the physiologic inflammatory cascade that occurs at the end of a normal pregnancy (Challis et al., 2009) could also generate depressive symptoms, thus explaining the negative relationship between gestational length and depression; that as depression increases, pregnancies get shorter. Stress induced depression has been a recognized phenomenon in the literature and is associated with numerous immunologic and neurobiologic changes (Southwick et al., 2005; Weiss & Goodman-Simson, 1985).

The understanding of what promotes versus inhibits fetal growth is much less developed. However, elevated cortisol levels are associated with increased vascular constriction (Girod & Brotman, 2004), and after bariatric surgery, people who are more depressed tend to lose more weight (Averbukh et al., 2003), suggesting that there are signaling pathways present in depression that interfere with nutrient exchange.

Predictors Can Be Risks At One Stage And Protective At Another

One of the most important extensions of previous knowledge by this study is the discovery of interplay, a sort of give and take, as a particular predictor moved from being a protective factor at one point in gestation to being a risk factor for lower birthweight and shortened length of gestation later in pregnancy or the reverse. This is seen for stress, partner support and other support.

By not studying the timing of these variables and their impact, important nuance in the PNI modulation of the pregnancy course has been inadvertently overlooked. Previous work on all of these variables has had mixed results. Some of this is due to use of different measures, or to power issues in the studies, but the current study establishes that some of the mixed effects are the result of timing.

Evolutionary thought has long recognized that compromise must be at the center of adaptive processes: "Adaptation, so far as that process involves the expenditure of energy, must go on in conformity with the principle of the conservation of energy" (Ryder, 1892, p2). Thus the finding that as pregnancy advances, a woman's social environment and her conscious and unconscious (PNI) appraisal of stress and its attendant inflammatory response can have paradoxical effects on birth outcomes,

protecting fetal growth at one stage while compromising it at another, or shortening length of pregnancy for a time, and then later protecting continued gestation, is not surprising. Throughout the pregnancy, the placental-maternal PNI system is constantly modulating, in effect evaluating the chance of reproductive success for this particular pregnancy. This modulation determines whether the uterine environment promotes early labor or inhibits it. And the placental level signaling regulates the placenta effectively withholding resources at some stages while advancing them to the fetus at others. This flexibility in direction of effect supports the adaptive reproductive framework over a biomedical one in which adverse outcomes are the result of broken physiology.

Outside of pregnancy, perceived stress and anxiety can be considered adaptive; the more alert you are to the risks in your environment, the better prepared you are to survive. Short term stresses are adaptive and enhance immune system responsiveness (Dhabhar, 2009; Dhabhar et al., 2010). Adaptive reproduction conceptually approaches stress in the same way. The stress response exists to promote reproductive success, not inhibit it. The more chronic stress that exists, however, the less capable the system is of maintaining the usual timing and behavior of signaling mechanisms that lead to normal weight babies being born at the completion of a normal length gestation.

It is unclear in these results whether or not the protective effect that stress has on birthweight for non-abused women in the third trimester is solely a result of a fit stress response, or if it also has to do with an evaluation by the placenta that given the metabolic resources that have already been devoted, the investment in the fetus's growth must be protected. It does appear however, that in the presence of perinatal IPV,

depression may induce a sort placental senescence throughout the pregnancy in regard to providing nutrients to the fetus.

McEwen and Wingfield's (2003) PNI stress processing theory that they call "allostasis" does not appear to be reinforced by this study. If allostatic load contributed to poor birth outcomes, then it seems that we would find stress and depression causing more substantial impact on birth outcomes as pregnancy progresses, but the impact of stress after 28 weeks is protective and when you evaluate the data according to time period, the association between depression and adverse outcomes is not present after 28 weeks.

Social Support Findings

The preservation of gestational length in the face of decreased partner support between 10-13 weeks can be understood as an adaptive response. Very little is known about the psychosocial or even the physiological exposures that induce spontaneous abortions in the first trimester, but it is plausible that this study suffers from a survivor's bias. The model did not include data from women who miscarried prior to 21 weeks gestation. It could be that many women with little social support from partners at this stage in pregnancy do experience early pregnancy loss. This would imply that the remaining pregnancies are somewhat hardy in the face of little social support. Pregnancies that survive in spite of abuse and lack of maternally perceived support are equipped from early in the pregnancy to complete a full term gestation. The longer the woman can stay pregnant, the more chance she has to deal with the stressors in her environment before she must turn her attention to the all-consuming task of caring for a

newborn. And if she is able to deal successfully with the sources of stress, presumably the newborn will be born into a safer environment, thus supporting the AR theory.

Longer gestations in women who have little social support provide a way for the mother to protect the fetus from the environment for as long as possible when there is little help available to her. It is certainly easier to protect oneself, than it is to protect oneself and a vulnerable infant while you are bleeding and perhaps otherwise compromised in the days and weeks following birth. So extending a gestation might be a strategy for protecting the offspring, in the hopes that more help will arrive before the labor must inevitably commence.

Social Support and Social Pressure Affect Reproductive Success

One of the tenets' of Wasser's (1999) evolutionary model of reproductive failure in humans is that social disarray is the leading cause of adverse birth outcomes in our species. He makes this assertion based on studies of other animals that are highly social, have dominant pair bonds and breed year round. Wasser and Barash, (1983) demonstrated that in primates "social pressure" is the most significant stressor determining reproductive success or failure. Thus, even though the finding that women with increased social support throughout gestation (with the exception of from 19-23 weeks) have decreased gestational length and/or birthweight may seem counterintuitive, it can be viewed as supportive of an AR framework.

Bullying, social status struggles within a group of co-workers or among women living together, or intense bereavement are all examples of these sorts of social pressures. The women in this study are all low-income, mostly unemployed tobacco users and 1 out

of 3 of them is being abused by their partner. The assessment of IPV is the only measure in this data set that addresses women's level of social disarray. But even for the women who are not abused, the exposure to tobacco suggests they are not the most physically fit women, and the demographic factors just discussed imply that they are probably not the socially dominant women in their environments, and may experience considerable social pressure. In other words, although these women perceived that they had support, it may have not been very functional support. It was this concept of functional social support from the closest people in a pregnant woman's social network that Wasser (1999) posited as the key to reproductive success.

For many years, social support has been viewed as a protective factor that can promote health, notwithstanding the presence or absence of stressors (Cohen, 1985). This is a foundation of social baseline theory (SBT)(Coan, 2010), which advances the idea that the presence and (functional) support of other human beings affect the way that our HPA system and our emotions are self-regulated. The current study affirms both of these ideas. Both partner support and other support is protective of gestational length at 19-23 weeks in the total sample. And for the group who is not abused, partner support is a critical positive predictor of gestational length in the third trimester. The protective effect of partner support, not surprisingly, did not exist in the subsample of women experiencing perinatal IPV, which is certainly a form of social disarray.

The IPV positive women in this study do experience some preservation of gestational length with increased support from others at 24-28 weeks. This support could be another key moderator in the relationship between depressive symptoms and

gestational length. Although depression has a much stronger effect than social support from others, perhaps the women with more functional support systems are less depressed. At a time when the inflammatory cascade is primed for activation, increased support in an otherwise chaotic social environment may help the regulation of immunoplacental functioning, thus preventing early activation of the inflammatory cascade.

In the current study, the finding among IPV exposed women that first trimester depression is associated with lower birthweight corroborates Elsenbruch et al's, (2007) results that first trimester depression was associated with lower birthweight in women. However, particularly among smokers, Elsenbruch's group found that (source unspecified) social support in the first trimester is an important buffer protecting babies from LBW and PTB, a finding that is not corroborated in the current study.

Social Support Measurement Issues

There are certainly examples in the recent literature of increased social support having a protective effect on birth outcome (Giesbrecht et al., 2013; Mirabzadeh et al., 2013; Wakeel, Wisk, Gee, Chao, & Witt, 2013). But there are also many examples of studies that have failed to find protective effects. Cochrane reviews, for instance, have repeatedly failed to find associations between social support and birthweight or gestational length, have focused heavily on interventions that involved prescribed informational type support (Hodnett & Fredericks, 2003; Hodnett, Fredericks, & Weston, 1996, 2010). Interventional studies examining social support usually examine the impact of a particular support action usually by nurses (e.g.Norbeck, DeJoseph, & Smith, 1996; Oakley, Rajan, & Grant, 1990; Olds, Henderson, Tatelbaum, & Chamberlin, 1986). In

work done by Olds et al, and Ickovics et al (2003, 2007), which found improved outcomes with social support interventions, the intervention was compared to outcome, but women's perceptions of social support level were not assessed.

The social support instrument utilized in this study, the Prenatal Psychosocial Profile social support subscales (Curry, Campbell, & Christian, 1994) focuses primarily on the emotional, and interventional aspects of social support (House, 1981), and very little on the appraisal and informational aspects of social support. Additionally, this current study along with the studies reviewed by Hodnett and colleagues (Hodnett & Fredericks, 2003; Hodnett, Fredericks, & Weston, 1996, 2010) did not examine attachment or evaluate the effect of social support systems on outcome. Cohen (1985) cautioned that evaluating perceptions of social support was particularly difficult because of the inability to control for the life stresses that individuals present with, which could confound the measurement. With this SEM, we were able to control for life stressors, perceived stress, cotinine and depression, and found that perceived social support from partners can shorten gestational length and support from others is associated with lower birthweights. What could not be accounted for in this study was the women's degree of functional access to healthy social networks, sometimes referred to as her personal social capital (Coleman, 1988). This social capital includes both community level variables but also the degree to which the woman can herself participate in the flow of community assets. A very depressed woman who does not work or interact with others may not have much social capital even in the midst of a highly functional community. But the BabyBEEP study occurred in a poor rural setting, where social capital was most likely a

rare commodity. It may be that social capital, and interventions designed to build social capital during pregnancy, are associated with improved outcomes, while perceived social support from others is less so.

Questions about process, how social support or social capital actually translates into well-being and better pregnancy outcomes, remain unanswered. Cohen (1985) suggested that when social interactions bolster or maintain self-esteem, this surely contributes to the positive effect of social support. Newer research suggests that the impact of social support occurs by increasing one's ability to self-regulate emotional responses to stressful events (Coan, 2008) and thus prevent PNI stress responses that affect health. These are the very types of questions being studied by SBT researchers today.

Impact of Timing on PNI of Pregnancy

This study advances our understanding of the PNI of pregnancy, by establishing that the neuroendocrine-immune-placental stress responses vary as the pregnancy advances. It suggests that the stress model proposed by Dunkel Schetter and Glynn (Dunkel Schetter & Glynn, 2010) is too simplistic, because it does not consider the changing placenta as an omnipresent and evolving moderator. It also does not consider that the changes in the perceptions and processing of the environmental stress are influenced from two directions. These changes could be due to changes in environmental stimuli, but they are just as likely to be changed by the evolving PNI-placental milieu of pregnancy. Other researchers, even ones who utilize PNI frameworks for their research into birth outcomes (e.g. Coussons-Read et al., 2012; Coussons-Read,

Okun, & Nettles, 2007; Coussons-Read, Okun, & Simms, 2003) have also not fully examined the potential impact of stage of pregnancy on effect of risks or protective factors. The work of Coussons-Read et al. (2007) looked only at a low risk sample of 20 women measured at various times across three trimesters, using categorical measures of social support, and did not find an association between social support and birth outcome. In Coussons-Read et al.'s 2012 work, the earliest gestational age was 10 weeks. The placental function prior to the 10th week EGA is distinctive; the physiologic milieu is starkly different during the early first trimester. This needs to be considered not just on a theoretical level, but on a methodological one as well.

The recent biobehavioral model that has been proposed by Wadhwa et al., (2011) favors a life-course approach to explaining birth outcomes. This group acknowledges the possibility that an individual's stress reactivity could change in pregnancy, thus affecting a particular outcome, but they seem to miss the implications of evolving placental function on that reactivity. They suggest that the life-course approach can help us understand reproductive success through both early epigenetic programming and amassed allostatic load. While epigenetic programming may be crucially important, this dissertation work, as described above, calls into question whether allostatic load is a useful concept in pregnancy stress research.

Nursing Implications

Theoretical Implications

The results of this dissertation work and supporting literature from other fields strongly suggest that efforts to improve birth outcomes should be evaluated from within

an evolutionary perspective such as that found in the model of AR set forth here. Biomedical frameworks do not provide an adequate context for understanding the impact that psychoneurological phenomena can have on pregnancy outcome. PNI mechanisms do provide a way to understand how the placental modulations can occur that produce various birth outcomes. These findings are consistent with the proposed theoretical framework of adaptive reproduction. They demonstrate that adverse outcomes such as lower birthweights and shorter gestational lengths are adaptive responses to environmental stimuli and that the responsivity varies according to gestational age. The discovery that timing is important in terms of how these prenatal risks and supports impact birth outcomes provides new opportunities for approach of these problems, beyond epigenetics, that can explain and potentially help resolve birth outcome disparities. Comprehending that the PNI mechanisms involved in both psychosocial and physiologic stress responses at the very least share similar timing, and perhaps are identical, is another critical step forward.

This study also offers apparent validation of SBT (Coan, 2010). SBT complements the theory of AR. The demonstration in the current study that at least during some stages of pregnancy (after 19 weeks) some types of social support are associated with improved birth outcomes, suggests that there are PNI links between people that not only help regulate emotion, but also contributes to the immunomodulation of the placenta that affects birth outcome.

Conceptualizing psychosocial variables, particularly around perceived stress, anxiety, the role of life stressors, social support/capital and the role of specific social

environmental threats or stresses need to be carefully considered moving forward. As adaptive models such as AR continue to demonstrate as seen in this study at the beginning of the third trimester, that being challenged by stress can build heartiness or resilience, it calls into question the usefulness of conceptualizing stress without any context for whether or not it causes undue hardship.

In addition, within subject variation in responses when performing psychoneurological measurements may not be entirely derived from external conditions or a woman's psychoneurological state. The role of the evolving placental endocrine and immune signaling is critical. Any attempt to understand the changes in a woman's perception of these variables as her pregnancy progresses must take the changing PNI milieu into account.

The protective impact of cotinine use in early third trimester for women experiencing perinatal IPV also challenges current thought about the role of tobacco use in pregnancy. It has been viewed as entirely noxious. But because of the role nicotine can play as a stimulant and regulator in those who are addicted to tobacco, and its inhibition of the inflammatory cascade, perhaps the role of smoking as a coping mechanism needs to be considered in the shaping of future theory on tobacco cessation during pregnancy. Particularly in marginalized populations, such as those experiencing perinatal IPV, the nicotine hit may be an important mood stabilizer or coping mechanism, making it not only more difficult, or more stressful to quit, but perhaps even riskier to the entire balance of cell-signaling mechanisms. This may seem heretical, but an evolutionary perspective such as AR demands that we consider what adaptive benefit continuing

smoking has to these pregnancies, and recognize that there may be negative as well as positive consequences to decreasing tobacco use in some women.

Depression, or depressive symptoms, also needs to be identified as an adaptive response. Both behaviors and psychoneurological states of being, symptoms or feelings can be adaptive. The bidirectional cell signaling that occurs in all human beings as we interact with the environment is continually unfolding. During pregnancy this signaling is made more complex by the presence of the placenta. When considering that the overall prevalence of antenatal depression is 20% (Bennett, Einarson, Taddio, Koren, & Einarson, 2004) and 45% in marginalized populations (Bennett, Marcus, Palmer, & Coyne, 2010), one has to consider what adaptive benefit these symptoms may have. These symptoms may be arising from cell-signaling at the level of the placenta. This is yet an unexplored area of PNI research, but given the relationships found here and elsewhere between depression and adverse birth outcomes, theory that utilizes a bidirectional understanding of depressive symptoms is clearly called for.

Thanks to evolutionary adaptive models, fever is now identified as an adaptive physiologic response. Pro-inflammatory cytokines increase and the body develops a fever, which is meant to help the body cope with an infection (Netea, Kullberg, & Van der Meer, 2000). Suppressing a fever may prolong the effects of the agent that stimulated it. Depression should also be considered as an adaptive response to environmental stressors. If, as AR posits, social chaos is one of the greatest threats to successful reproduction, is it any wonder that a socially marginalized woman, in a chaotic situation, responds by developing symptoms meant to isolate her from the group? The social

isolation caused by depression may actually improve her ability to self-regulate and enhance her fetus's chances of survival.

Another situation in which depression may be adaptive is in the case of a woman carrying a fetus that is not developing properly. This researcher has cared for two women with depressive symptoms in their early pregnancies who have reported feeling "disconnected" from their pregnancy, only to find out in late second trimester or beyond that the babies they carried had anomalies that were incompatible with life. Perhaps the symptoms that made them feel disconnected emotionally stemmed from placental signaling that stunted their emotional response in view of a pregnancy that is unlikely to produce a viable offspring.

On the other hand, given the bidirectional nature of this adaptive depression response, the perception of being in a deprived environment may trigger a placental signaling response, causing depressive symptoms even when there is no deprivation or threat! This may be a key to understanding how anxiety is related to preterm birth, and why pregnancy related anxiety seems to be particularly connected to this phenomenon.

The protective nature of stress on birthweight at 29-31 weeks, and the paradoxical behavior of social support variables in this study demonstrate the adaptive nature of the systems' responses. Perhaps even a physical stressor, such as the common complaint in the first trimester, nausea, could be an example of another placental signaling driven adaptation, another protective event. Practitioners often tell women that intensive nausea is a sign of a healthy pregnancy. Nausea could be adaptive in two ways. First, it can protect the woman from consuming contaminated or unhealthy food. But it also creates a

ketotic state that has been associated with neurodevelopment (Mantis, Fritz, Marsh, Heinrichs, & Seyfried, 2009). The experience of nausea may represent functional signaling processes at work to create a hardy, healthy pregnancy.

Methodological Implications

Before addressing six methodological considerations for future research aimed at promoting healthy birth outcomes, the contributions of this current study to nursing methodology should be acknowledged. This dissertation project contributes and advances nursing research by utilizing a multilevel modeling technique of an existing data set using structural equation modeling with planned missingness. This innovation allowed the comparison of categories that did not exist in the original dataset, and has provided helpful insight regarding stress processing in pregnancy. The utilization of these complex modeling techniques shows promise for evaluating many types of health outcomes.

This multilevel model did not examine the individual differences in change over time; the seven gestational age groups were categorical, not continuous. Latent growth curve modeling is an obvious next step for modeling PNI interactions during pregnancy with birth outcome. Using these techniques with existing data sets is a cost-efficient and time efficient way to gain new knowledge about the PNI and birth outcome variables of interest.

Also, future research needs to be designed to carefully consider whether the birth outcomes we measure truly give us a picture of the offspring's own evolutionary fitness and how likely they are to be reproductively fit themselves. It makes sense to

acknowledge that birthweight and gestational lengths are signs, risk factors in their own right that suggest likelihood of morbidity. Going forward it seems that infant or child neurodevelopment is a better measure of long term health of the child than simply evaluating birthweight or length of gestation. Of course the latter are the far easier outcomes to assess.

Thirdly, in order to develop a comprehensive understanding of the interplay between adverse birth outcomes, pregnant women need to be studied from as close to conception as possible. Prospective work with multiple measures of community level, and nuclear social behavioral variables including measures of social capital, psychological variables and biomarkers will provide the most comprehensive picture of how these multilevel variables interact. Ideally women would even be identified prior to conception, but enrollment at the time they present for care with a positive pregnancy test would be preferable to waiting until the initial prenatal evaluation by a nurse-midwife or physician, which usually doesn't occur until the very end of the first trimester. These results demonstrate that biopsychosocial models (Dunkel Schetter, 2011) and PNI frameworks (Christian, 2012; Latendresse, 2009) need to account for the evolving placental cell-signaling mechanisms that affect the maternal and fetal immunomodulation. The timing of stressors, perceptions of stress and the resulting anxiety, and the presence of social support are crucial influences on both the inflammatory cascade leading to birth and the signaling that directs fetal growth. This timing should be accounted for in study designs.

It is important to carefully conceptualize social support, but this is not enough. It must also be carefully measured. The current study showed a relationship between perceptions of social support and outcome. To better delineate the nature of this relationship, future research needs to measure baseline social capital, interventions and the levels of support women perceive as they move through a pregnancy while receiving these interventions. Perception of social support is an important mediator in any interventional research and will help better develop the relationship between SBT and the PNI of pregnancy.

In addition, study interventions should attempt to include components of social support beyond providing information and physical resources. Elusive emotional components of social support such as sharing and processing experiences together, and appraisal components such as providing comparisons or constructive feedback need to be clearly operationalized. This calls for qualitative work that can be followed by quantitative work to identify how individual nurses, nurse-midwives and other care providers during the perinatal period commit the act of caring in ways that are actually perceived as caring by the recipient. We do not know exactly what makes a nursing intervention intended to demonstrate caring and support effective. But it is essential that the choices in method allow the possibility of discovering these rather intangible processes.

One further methodological implication extending from this study is that interventions aimed at decreasing adverse birth outcomes that arise in the population of women experiencing perinatal IPV do not need to consist exclusively of women who

have screened positive for IPV at enrollment. Stress and dysfunctional or chaotic social networks can have a negative impact on any pregnancy. Effective support interventions aimed at promoting the health of the woman and her pregnancy (as opposed to decreasing violence) can improve outcomes for women who are experiencing stress, anxiety or depression regardless of the type of stressors involved. Screening repeatedly throughout the study can improve identification of the women in the study who actually are abused, as was done in BabyBEEP.

Policy Implications

There are several policy level propositions stemming from this current study that would help meet the goal of reducing disparities in birth outcomes related to stress exposures in the perinatal period. None of them are simple or inexpensive, because they involve systems level changes.

The discipline of nursing has struggled for the past thirty years or more to figure out what theoretical perspective can best differentiate it from medicine and best move the science of nursing forward. An important implication of this work for the discipline of nursing is the advantage of embracing evolutionary models such as AR to help understand and address health disparities and alterations in individual wellness. A policy shift is called for, away from biomedical frameworks, instead studying mechanisms as bidirectional systems aimed at providing selective advantage for reproduction for the most reproductively fit individuals. Nursing interventions could then be designed to maximize fitness and compassionately approach problems that result from being overwhelmed by environmental challenge. Developing curriculum utilizing evolutionary

biology as the underlying framework would represent a fundamental policy shift in how advanced practice nurses are educated. These are promising frameworks, however, and should be pursued not just in the name of improved maternal and child health, but to promote wellness in general.

Shifting away from biomedical explanations for poor reproductive outcomes will empower nurse-midwives and maternal child health nurses to return to their public health roots. The systems that need to be supported or changed are not isolated individuals in an AR framework, but are global, and raise questions and ethical choices about the consequences of our systemic manipulations. Nurses are well-positioned to help negotiate these discussions on a policy level.

There are several specific types of programs that the AR framework supported by this dissertation data suggests. For instance, federal mandates that would ensure that women would have access to a full range of contraceptives and family planning opportunities regardless of their employment status or type of insurance should be considered an essential first step in providing comprehensive preconceptional care. This would provide a safeguard for women and their partners, leveling opportunity to avoid the potential burden of childbearing when they are unprepared to do so. This strategy has long been recognized as an important step in improving women's and children's health worldwide (World Health Organization, United Nations Population Fund, & UNICEF, 1989) . The ACA (2010) has provisions to make contraceptives more readily available, but this has been challenged in court (Liptak, 2013; Somashekhar, Barnes, & Boorstein, 2014).

The finding that social support in the second half of pregnancy, especially from partners, has a positive impact on both birthweight and length of gestation suggests that we need to equip those partners with the skills to provide adequate or even premium support. Funding for the development and implementation of comprehensive family planning/ sexual education curriculums in the public schools promoting the message that every pregnancy should be a planned pregnancy and that partnering in parenthood begins at conception, would set the stage for prenatal support in a way that current public health messages in these contexts do not. The message promoted by "Baby think it over"(Barnett, 2006) and other infant or pregnancy simulation programs is that caring for a newborn is hard work. The message that parenting is easier and healthier for babies and for their mothers when a partner commits to the process with you before conception is more effective when coupled with the teaching of strategies for having conversations about these issues before coitus. This should be recognized as an important step in preconceptional care.

Involving partners in fathering programs that promote the idea that how well they support their pregnant companion directly affects the health and strength of their newborns could have tremendous impact. But the informational campaigns are only a superficial first step. Providing partners with opportunities to learn and practice specific supportive communication and interactional strategies could make a tremendous difference, particularly for women who live in otherwise socially chaotic environments. These programs would need to be culturally acceptable, relevant and engaging.

Programs equipping expectant partners with social support skills could have significant impact, especially in vulnerable populations. In the early 1970's there was a cultural revolution in child-bearing in the United States; partners began accompanying pregnant women to childbirth classes and into the delivery room. Creating new prenatal care structures that include partners in more intensive prenatal care programs is certainly a public health challenges but it is not without a precedent of success.

Other preconceptional programs, aimed at building self-esteem, and increasing stress heartiness of childbearing aged women, and providing them with opportunities to practice communication and relationship strategies are other ways to help level the differences in vulnerability that exist among this population. Many other nations have prenatal and maternity and paternity leave programs, for instance, that preserve parents' jobs and provide financial support during pregnancy for all women. In contrast, in the United States, women who are the most educated have the most access to paid maternity leave benefits; leaving more economically vulnerable women with fewer options for managing work life balance during and after pregnancy (Laughlin, 2011). Studies show that paternity leave programs not only help men but help women (Mundy, 2014).

Additionally, given the positive effects of mid-pregnancy support from others found here, this study substantiates the need for continued and enhanced funding for nurse and nurse-midwifery led support interventions during pregnancy that have been shown to improve birth outcomes. These include telephone support (Bullock, Wells, Duff, & Hornblow, 1995), nurse home visiting programs(Kothari, Zielinski, James, Charoth, & Sweezy, 2013; Oakley et al., 1990; Olds et al., 1986), home visiting by

paraprofessionals (Katz et al., 2011) and group prenatal care(Ickovics et al., 2003, 2007; Little, Motohara, Miyazaki, Arato, & Fetters, 2013; Tanner-Smith, Steinka-Fry, & Lipsey, 2013). The Affordable Care Act (2010) and Centers for Medicare and Medicaid Services (2012) took steps to evaluate and implement these programs, but the funding for all of them is due to run out by 2016.

Nurses need to advocate for the families in their care, by educating legislators and other policy makers about the importance of reimbursing for these types of nursing interventions. Structural changes can create more supportive environments in which we can conceive and raise the next generation. When nurses embrace public health legislative advocacy as not just a professional duty, but an important nursing intervention on behalf of the families they care for, not only will the political power of the profession increase, so will the impact of their care.

Clinical Implications

Nurses and nurse-midwives can derive several clinically relevant implications from this study. Nursing interventions such as telephone support, nurse home visiting and group prenatal care models are clearly important tools that are can improve the health of mothers and babies, and we need to be providing more of these types of interventions. In addition, public health interventions that foster a sense of community and provide increased social supports should be pursued, particularly among those populations more vulnerable to birth outcome disparities. Especially in light of studies that suggest that treating depressive symptoms in pregnancy with selective serotonin reuptake inhibitors does not improve birth outcomes (Latendresse & Ruiz, 2011), this study implies that

social support interventions, particularly those that teach skills and enhance social network functioning in order to better cope with stress, are the best tools we have to combat adverse birth outcomes. This study adds to the evidence that enhancing a pregnant woman's sense that she has social support, and encouraging skills aimed at reducing perinatal IPV, are important nursing strategies that will maximize healthy birth outcomes.

This study further suggests that prenatal education efforts in the first trimester should be redirected away from smoking cessation towards bolstering stress management and social support resources. This study suggests that interventions are time sensitive and early interventions are important. Evidence based interventions aimed at increasing self-esteem and stress hardiness should be implemented and completed by the 24th week gestation mark. Nurses and nurse-midwives should seek out interventions that can enhance women's perceptions of social support as they move into mid-pregnancy. Specific coping strategies to deal with stress early in pregnancy should be taught, recognizing that social support and averting depressive symptoms provides a degree of protection against adverse birth outcomes.

Women who develop medical complications of pregnancy that are more related to physiologic stresses also need nursing attention directed at the state of their psychoneurological health and their social environment. Any care that nurses can provide to support psychoneurological wellness, decreased perception of stress and symptoms of depression could potentially impact the outcome of these pregnancies.

At the same time, these study findings offer an explanation for why socially vulnerable populations of pregnant women seem to have worse outcomes when they experience physiologic complications of pregnancy. These findings emphasize the importance of providing vulnerable populations premium prenatal care, including comprehensive preconceptional care, early enrollment in prenatal clinics, group care models, telephone support and home visiting.

Limitations

There are numerous limitations to this research, stemming from the use of secondary data, and the research methodology. The sample population was homogenous; all smoked before and during pregnancy, were low-income, rural and overwhelmingly Caucasian. Information about the sample populations co-morbid medical and mental health issues, antidepressant use, availability of and utilization of community resources, and overall safety of the communities in which they lived was not available in the data set and should be considered as potential confounders that could not be controlled for in this study. There were not any variables in the BabyBEEP dataset that could be used to measure or model stress reactivity. This is an unfortunate limitation of this research, as much of the debate in both the biomedical and PNI literature about stress and adverse birth outcomes is focused on stress reactivity as a way to understand the signaling mechanisms involved.

As discussed in Chapter 3, the inability to model severity of abuse is a limitation, which meant that abuse had to be measured as a dichotomous event. Future research should utilize measures that would capture severity data. A latent construct that could

model stress as both perceived stress, perceived life stressors and overall severity of exposure to a particular stress (in this case, perinatal IPV), could help to further our understanding of the nature or sources of discrepancies in outcome that has plagued the stress in pregnancy and depression in pregnancy research to date.

Only 18 percent of the study population in BabyBEEP was enrolled prior to 9 weeks gestation and 52 percent were enrolled before 14 weeks gestation. It is possible that we have missed the full extent of first trimester risk exposure to unfavorable environmental stimuli.

There were compromises made to accommodate the categorical use of only 7 gestational groups during the restructuring of the data set. These could potentially detract from the validity of these findings. When there were multiple cotinine measurements in a particular group, both cotinine measurements were dropped from the final data set. There were also about 5 cases that were dropped from group 5 because they were interviewed twice during this time period, first for their baseline interview at 24 weeks and then at a 28 week visit.

In spite of the strong evidence of significant results found in this modeling process, there are several issues related to the SEM process that might raise questions about the validity of these findings. The use of clustered groups in which there was a great deal of missing data, rather than a single longitudinal cohort is an important limitation. The power analysis calculated in Chapter 3 established that significant results in this study would not be attributable to overpowering. The model is powered to find a statistically significant answer to the hypotheses set forth; however, the study is

underpowered to find statistical significance in the individual paths between predictors and outcomes. Statistical significance that is found in this model is sound, but the model is underpowered to protect against Type 2 error (protect against false negatives). A prospective longitudinal study that examined every woman on a monthly basis throughout pregnancy would provide a better powered study from which absolute goodness of fit measures could be calculated. Because of the degree of empty cells in each group, the modeling software could not produce absolute measures of goodness of fit. Thus AIC and minus 2 log likelihood measures were used to assess fit and these are both approximate indicators, rather than absolute.

Perhaps the structural equation model would have been better evaluated on a measurement level, had a confirmatory factor analysis (CFA) been done on each of the social support subscales (partner and other) from the Prenatal Psychosocial Profile (PPP), and then partner support and other support could have been treated as latent constructs. This was not done for two reasons. First, because the PPP has already been established as a reliable and valid instrument (Curry et al., 1994). Secondly, the separation of these subscales was not in the original conceptual model, and only occurred during model trimming, when the direction of the latent construct estimates was in opposition to other literature. The data had already been restructured using calculated total scores from the PPP subscales. To run a CFA on these would not have been quickly accomplished; it would have required another round of data restructuring in order to evaluate these as latent constructs.

The model trimming step of SEM was cut short in the results section, primarily because of the desire to preserve the theoretical conceptual model to the largest extent possible. The model was never constrained to include significant estimates only. Nor were further models run assessing each predictor separately. These models would provide further information about the relationships between the predictor variables and the outcomes, as they would have more power than the full model. However, these types of models would not be controlling for the other predictors, which are real predictors that affect birth outcomes. This modeling also purposely avoided looking at correlations between predictor variables, and correlations between the outcomes; thus indirect effects were not evaluated. This limitation was imposed based upon the chosen hypothesis. The

goal of this study was not to evaluate individual direct and indirect effects, but to test whether timing made a difference in outcome. These are all notable limitations to consider when interpreting these findings.

Future directions of research

Although this study adds to the understanding of how psychosocial stressors impact birth outcomes, more research is needed to clarify the complexities of environmental influence on maternal-placental HPA activation, develop intervention strategies, and create therapeutic environments for at-risk pregnant women that may improve maternal and infant health. The logistical challenges presented by these study questions are great but not insurmountable. In the quest to provide all children with the healthiest start possible, these challenges ought to be embraced in future research.

Immediate next steps

The model trimming steps described under the limitations above will provide a complete and final result to this SEM process using categorical group level data. This is an obvious next step.

One of the other initial follow-up steps will be to attempt replication of these results through an analysis of a different population of women, using the most parsimonious, fully trimmed model. Replicating this study in a larger and more heterogenous population will establish the generalizability of these effects. There is a theoretical possibility that the timing will not be the same in other ethnic groups, especially in those with higher risk of adverse birth outcomes. An interesting possibility for this replication study would be the DOVE data (R01 NR009093).

It would be very interesting to try to replicate the social support results in other cultural environments. In our cultural context the strong nuclear family construct is held as an ideal. It is possible that partner support is a cultural artifact that will not be as significant in cultures that feature more gender segregation or place more emphasis on intergenerational or age-cohort same sex supports.

An additional immediate next step is to evaluate this same model of psychosocial variables with the 24 month neurodevelopmental outcomes available in the Baby BEEP for Kids (NIH:HD04554) dataset for a subset of the 325 children born of BabyBEEP subjects. Ascertaining whether the predictor variables significantly impact neurodevelopment in similar patterns of effect is an important next step. Epigenetic changes in infants' PNI signaling and neural processing may occur in utero and be influenced by these same PNI changes related to psychosocial variables. Documentation of the timing of these changes will allow a whole new layer of "early intervention" programs; they could begin in utero.

Given the protective effects in mid-pregnancy on birth outcomes provided by social support (and end of pregnancy effects for partner support), and the apparent defense this provides for SBT, this presents an opportunity to test the extension of one of SBT's suppositions, whether or not functional social support causes decreased stress reactivity during pregnancy. A test of this would also need to be longitudinal to try to capture changes in reactivity across gestation.

Short term (3-5 year goals)

Following validation of this model, this researcher would like to assemble a collaborative research team to pilot a multi-arm interventional study that would include women in group prenatal care, and women in traditional prenatal care programs, as well as those involved in prenatal home visiting programs conducted by nurses and community health workers. Ideally enrollment would begin at the time of pregnancy confirmation. This would help establish whether or not there is a group in which increased environmental or psychosocial stressors in the first trimester actually leads to early pregnancy loss.

Given that perception of increased stress is detrimental to birthweight in mid-pregnancy, interventional research is needed that can contribute to coping skills and resiliency techniques in the first trimester, in an effort to increase fitness for dealing with stress as the women enter vulnerable periods of pregnancy. Programs aimed at enhancing communication and partner support throughout the pregnancy should also be evaluated to determine if these utilizing these strategies might protect pregnancies from adverse outcomes, particularly in the most vulnerable populations.

Opportunities to do multidisciplinary research, combining these intervention studies with placental cell-signaling research conducted by biologists and/or other neural imaging research on social attachment could elucidate some of the underlying mechanisms of placental signaling and point towards other types of intervention. Another intriguing avenue for investigation, if future studies corroborate the 24-28 week and 29-31 week windows as critical periods for stress processing in pregnancy, will be to

determine what the PNI signaling activities are that occur at these times; what changes at the end of the 29th week to make pregnancies more resilient to stress?

Studies also need to be done to evaluate what precisely it is about social support or capital that improves or hurts outcomes. How much do community level variables matter? Is it the presence of trusting relationships, intimacy, having a sense that there is help if you need it, or is it some aspect of integration into a social community that makes a difference? Does there need to be a sense that the people providing you with support have some level of life competence themselves, or do they need to provide some sort of functional assistance in order to be protective?

Another interesting research question stemming from this and other research has to do with the prevalence of antenatal depression. Measurements of depressive symptoms in the first and third trimesters may be exacerbated by the normal inflammatory processes of these stages in pregnancy. Teasing out the level at which this moves from being normal adaptation that should be allowed to run its course, to a depression that requires action on the part of health care providers in order to preserve the health and well-being of both mother and child, will be challenging.

An additional question involves what, if any, differences there are between familiarly, or communally acquired social supports versus those that are therapeutically contrived. How much impact the health care system can have on birth outcomes in isolation from the rest the society's structure, remains to be discovered. Another avenue of research to consider concerns the impact that community rather than individual level resources have on these outcomes. Are there cell-signaling differences or timing

differences in the way affluent pregnant women in a resource rich environment process environmental stimulus during pregnancy? In animal models, some females in the social group do have successful pregnancies in the midst of environmental stresses, and some do not. Disentangling what is epigenetically prescribed prior to the pregnancy and what is processed through PNI mechanisms during the pregnancy is work for future generations of researchers.

A further possible research venture stemming from this work could be an interventional study with pregnant smokers. Specifically, the interventions could include providing enhanced social supports in the first trimester and stress management techniques, along with smoking cessation strategies.

Conclusion

This is a transitional era for prenatal care. On paper, the leading public health agency in the United States has defined preconceptional health services as a part of prenatal care; however, the funding to implement this policy has not yet been mandated. The expansion of this definition is intended to improve maternal and infant health. The data modeling in this study supports the understanding that prenatal care is not an end in itself, but exists as a supportive presence that contributes to people's abilities to lead good lives. For a pregnant woman, this includes the ability to reproduce successfully.

Utilizing an adaptive reproductive framework to examine birth disparities is an important step forward. Future work on the nature and timing of these mechanisms is critical to the development of interventions that can reduce disparities in birth outcomes. Antenatal stress does not always lead to poor outcomes; sometimes it creates hardiness.

Determining how to capitalize on the advantage of social supports while creating resilience for acute stress processing can enhance the probability of reproductive success in the most vulnerable populations.

Perhaps this study leads us to another proposition; that the theoretical conceptual model was not the best representation of the adaptive reproductive framework that describes adverse outcomes. Depression especially, long thought of as a risk factor that leads to adverse birth outcomes, needs to be reconsidered. Depressive symptomology is itself an adaptive strategy. Environmental exposures, sometimes fetal in origin, sometimes maternal in origin, sometimes externally imposed, change the cell signaling in ways that make a pregnant person feel depressed. And while there are medications that may improve some symptoms of depression, they do not "fix" the underlying placental signaling that contributes to these symptoms, since they do not change the other adverse outcomes. Furthermore, low birthweight and preterm birth are not outcomes that are ends in themselves, but they are risk factors for increased morbidity and mortality.

As we move forward in nursing research and practice, maternal child health efforts need to be refocused on preventing these depressive symptoms from appearing in the first place, decreasing infant morbidity and maximizing children's developmental outcomes. This appreciation of adaptive reproductive processes; how adverse birth outcomes occur in part because socioenvironmental conditions are not optimal, needs more careful scrutiny. But it also presents all manner of opportunities to change the way we teach future maternal child health nurses and nurse-midwives to provide prenatal care, and provides leads on important preconceptional care that goes beyond vaccinations and

screening for infection to structural change that can improve the health and success of the most vulnerable families.

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