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Examining Biological and Psychological Variables in Hypertensive Disorders of Pregnancy

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EXAMINING BIOLOGICAL AND PSYCHOLOGICAL VARIABLES IN HYPERTENSIVE DISORDERS OF PREGNANCY

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing at the University of Kentucky

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2017

ABSTRACT OF DISSERTATION

EXAMINING BIOLOGICAL AND PSYCHOLOGICAL VARIABLES IN HYPERTENSIVE DISORDERS OF PREGNANCY

Despite advances in obstetric care, hypertensive disorders continue to complicate pregnancies at a high rate. Worldwide, hypertensive disorders affect up to 10% of pregnancies. The United States has seen a 25% increase in the incidence of hypertensive disorders over the last two decades (American College of Obstetricians and Gynecologists, 2017). These complications constitute one of the greatest causes of maternal and perinatal morbidity and mortality with an estimated 50,000 to 60,000 deaths per year across the world (American College of Obstetricians and Gynecologists, 2017). Although the etiology of hypertensive disorders remains unclear, there may be an association with both maternal biological and psychological distress in the development of the disorder. Although both distress and biomarkers have been identified in association with a hypertensive disorder, little data exist examining the components of distress and the alterations in biomarkers in women developing these disorders. Due to the limited evidence, a critical need exists to examine the relationship of perceived maternal distress and biomarker measures in the development of a hypertensive disorder during pregnancy in order to better understand this phenomenon.

The purposes of this dissertation were to: 1) understand the experience of having a hypertensive disorder during pregnancy; 2) to investigate the association of perceived stress and changes in immune response via biomarker measures in women who develop a hypertensive disorder during pregnancy; 3) to review, summarize, and evaluate the literature examining the relationship between perceived maternal distress (stress, anxiety, and depression) and the development of a hypertensive disorder; and 4) to investigate the association of perceived distress in the development of a hypertensive disorder during pregnancy.

Data obtained from a qualitative study of women with a hypertensive disorder during pregnancy placed on bed rest reported several stressors associated with the experience. These stressors related to differing and often conflicting management plans by different providers and not feeling providers heard their concerns. The evidence supports these women experience stress during this pregnancy complication. Analysis of data obtained at each trimester of pregnancy did identify differences in biomarker levels

based on perceived stress and women with a hypertensive disorder and those without a hypertensive disorder. Evidence from a systematic review of literature supporting maternal distress in the development of a hypertensive disorder was mixed. However, few studies existed and of those reviewed, most lacked rigor. Analysis of data obtained early and late in pregnancy did not indicate a relationship between psychological distress and the development of a hypertensive disorder in pregnancy. Women with a higher BMI were 12% more likely to develop a hypertensive disorder.

The factors associated with the development of a hypertensive disorder are complex. Maternal perceived stress and inflammatory responses differ between women with a hypertensive disorder and those without a hypertensive disorder in pregnancy; however maternal distress did not differ between groups. Body mass index was associated with the development of hypertension in pregnancy. Clinicians need to include assessment of maternal BMI as a modifiable risk factor in the development of a hypertensive disorder during pregnancy. In addition, although psychological distress was not associated with the development of a hypertensive disorder, women still suffer with components of distress. Clinicians could identify and support women experiencing distress thereby promoting a healthier pregnancy.

KEYWORDS: Maternal Distress, Hypertensive Disorder in Pregnancy, Biomarkers

Stephanie A. Kehler

4/24/17

EXAMINING BIOLOGICAL AND PSYCHOLOGICAL VARIABLES IN HYPERTENSIVE DISORDERS OF PREGNANCY

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4/24/17

This dissertation is dedicated to my husband who supported me when I went back to school and continued in graduate school. And to my children who were understanding when mom wasn't home as much as she used to be. I love you all dearly.

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“All those who are around me are the bridge to my success, so they are all important.” Manny Pacquiao

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Chapter I: Introduction

Background

Hypertensive disorders in pregnancy occur in 5-10% of all pregnancies in the United States (Kuklina, Ayala, & Callaghan, 2009). These disorders are one of the greatest causes of maternal and perinatal morbidity and mortality. In the United States, the rate of pregnancy-related mortality from hypertensive disorders was 7.6% in 2012 (Centers for Disease Control and Prevention, 2016).

Hypertensive disorders in pregnancy can be classified into four categories: 1) preeclampsia-eclampsia, 2) chronic hypertension, 3) chronic hypertension with superimposed preeclampsia, and 4) gestational or pregnancy-induced hypertension (American College of Obstetricians and Gynecologists, 2013). Preeclampsia is one of most serious form of hypertensive disorders during pregnancy. The rate of preeclampsia in the United States has increased 25% in the last two decades resulting in becoming the leading cause of maternal and infant illness and death (American College of Obstetricians and Gynecologists, 2017).

Researchers have reported a maladaptive maternal inflammatory response may play a role in the development of a hypertensive disorder during pregnancy. A systemic inflammatory response is common to all pregnancies and changes throughout pregnancy; however, an increased pro-inflammatory response has been associated with the development of a hypertensive disorder (Moreli, Ruocco, Vernini, Rudge, & Calderon, 2012; Palm, Axelsson, Wernroth, Larsson, & Basu, 2013; Szarka, Rigó, Lázár, Bekő, & Molvarec, 2010). Furthermore, maternal psychological distress (stress, anxiety, and depression) has been associated with this high-risk pregnancy and may influence maternal inflammatory response (Franco, Ferreira, Vieira, & Silva, 2015; Kurki,

Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000; Qiu, Williams, Calderon-Margalit, Cripe, & Sorensen, 2009; Yu et al., 2013; Zhang et al., 2013).

The purposes of this dissertation were to: 1) explore the experience of having a hypertensive disorder during pregnancy; 2) to investigate the association of perceived stress and changes in immune response via biomarker measures in women who develop a hypertensive disorder during pregnancy; 3) to review, summarize, and evaluate the literature examining the relationship between perceived maternal distress (stress, anxiety, and depression) and the development of a hypertensive disorder; and 4) to investigate the association of perceived distress in the development of a hypertensive disorder during pregnancy. Four manuscripts, one addressing each purpose, are presented in Chapters Two through Five.

Summary of Theoretical Framework

The first framework utilized was developed by Lazdam et al. in 2011. This framework illustrated maternal inflammatory response and its relationship to the symptoms of preeclampsia, which is primarily endothelial dysfunction (Lazdam et al., 2011). The framework associated both maternal factors and systemic inflammatory response to endothelial dysfunction in addition to several other factors. However, the focus of this framework was the symptoms of preeclampsia and not preeclampsia itself or gestational hypertension so a more comprehensive model was needed that included other forms of hypertensive disorders.

The psychoneuroimmunology framework (PNI) is a more comprehensive model that illustrates associations between psychological distress, immunity or inflammatory responses, and pregnancy outcomes including hypertensive disorders of pregnancy

(Christian, 2012b; Coussons-Read, Okun, & Simms, 2003). The pathway of the psychological distress is by way of the sympathetic nervous system and activation of the hypothalamo-pituitary-adrenal axis thereby altering the inflammatory response leading to adverse pregnancy outcomes. The framework consists of environmental stressors moderated by coping resources and leading to psychological distress. Psychological distress may affect immune function directly or through health behaviors. In turn, immune responses or inflammatory responses may affect maternal health (hypertensive disorders). Within the PNI framework, the construct of psychological distress included perceived stress, general anxiety, and depressive symptoms. Furthermore, the concept of psychological distress is on a continuum with low stress at one end and anxiety or depression at the opposite end (Emmanuel & St John, 2010).

This more comprehensive model provides a valuable framework for the explanation of how stressors and psychological distress can impact hypertensive disorders in pregnancy. In addition, it also allows for future interventional studies related to coping resources and health behaviors.

Chapter Overviews

Overview of Chapter Two

Preeclampsia is a hypertensive disorder in pregnancy that can put a women and fetus at risk for adverse outcomes (American College of Obstetricians and Gynecologists, 2013). Women with preeclampsia often experience both a physical and psychological hardship in these pregnancies (Malakouti, Sehhati, Mirghafourvand, & Nahangi, 2015). Psychological issues, including stress and anxiety are often exhibited in this population

partly due to the management of this high-risk condition including prolonged bed rest (Rubarth, Schoening, Cosimano, & Sandhurst, 2012).

Bed rest as a treatment modality for preeclampsia was first documented in the 1950's (Morris, Osborn, Wright, & Hart, 1957) and continues to be recommended as a treatment for the progression of preeclampsia. Researchers have reported up to 93% of maternal fetal medicine physicians and obstetricians have prescribed bed rest despite the latest recommendations from ACOG (American College of Obstetricians and Gynecologists, 2013; Bigelow & Stone, 2011).

Although researchers have reported about the experience of preeclampsia women placed on bed rest, the psychological and emotional support these women may need has not been thoroughly documented. In addition, the author could not find any qualitative research related to preeclampsia and bed rest after the new 2013 ACOG guidelines were released. In Chapter Two, a qualitative descriptive approach provided a comprehensive summary of the experience of having preeclampsia and subsequently being placed on bed rest in 2015. As a result of this study, women experienced a variety of stressors most similar to ones women reported 20 years ago. Healthcare workers should take a more pro-active approach in assessing and addressing the psychological needs of these women. Future research should focus on stress reduction strategies for these women. Additionally, as healthcare delivery and management of preeclampsia continues to evolve, clinicians should incorporate evidence-based practices and communicate these practices to the women they treat thereby potentially reducing maternal stress and anxiety.

Overview of Chapter Three

Hypertensive disorders in pregnancy are common complications occurring in five to ten percent of pregnancies in the United States (Kuklina et al., 2009). Although the exact mechanism underlying hypertensive disorders in pregnancy, there is evidence of the involvement of a maladaptive maternal inflammatory response (Eiland, Nzerue, & Faulkner, 2012; Palm et al., 2013; Ramma, 2011). Preeclampsia is associated with an overall pro-inflammatory response with elevated amounts of pro-inflammatory cytokines (Szarka et al., 2010). These serum biomarkers provide a quantifiable measure of the inflammatory response.

Perceived maternal stress experienced during pregnancy can increase the risk of preeclampsia (Zhang et al., 2013). Researchers proposed the hypothesis that maternal perceived stress during pregnancy has a negative effect on pregnancy outcomes by altering maternal inflammatory response (Coussons-Read, 2012). Elevated perceived stress was related to higher levels of biomarkers early and late in pregnancy (Coussons-Read, Okun, & Nettles, 2007). However, most studies of maternal stress and the inflammatory response in the development of a hypertensive disorder are cross-sectional. In addition, biomarker measures are not consistent across studies and conclusions about their importance equivocal. Bridging the gap between maternal stress, inflammatory response and early detection of a risk of a hypertensive disorder could improve pregnancy outcomes in this population by identifying those women at an increased risk and allowing possible interventions to reduce the risk.

A secondary data analysis from a prospective non-experimental study of culturally and ethnically diverse women recruited from three prenatal clinics was

conducted (Ashford et al., 2015). In this investigation, a 1:2 cases control design was used. Cases were women diagnosed with a hypertensive disorder of pregnancy and controls were women without a hypertensive disorder matched on age and parity. Study measures were collected at each trimester of pregnancy. Systemic inflammation was measured with biomarkers, specifically both pro- and anti-inflammatory cytokines. Stress was measured through the Everyday Stressors Index (ESI) (Hall, 1983). Results of these analyses determined no significant differences in inflammatory biomarkers between hypertensive and normotensive groups in each trimester. When stress was dichotomized, there were differences inflammatory biomarker levels within these groups. The interaction of stress level, hypertensive status, and trimester was significant for one inflammatory biomarker, IL-10.

Overview of Chapter Four

Chapter four provides an investigation of the current literature related to the association between psychological distress and the development of a hypertensive disorder. Maternal psychological distress conditions including stress, anxiety, and depression has been associated with hypertensive disorders in part through maternal dysregulated inflammatory response (Vianna, Bauer, Dornfeld, & Chies, 2011).

Prevalence of psychological distress in pregnancy has been reported between 13 and 25% (Çapik & Pasinlioglu, 2015) with stress being reported most often. The March of Dimes indicated nearly 75% of women experienced at least one stressful event in the 12 months prior to delivery (March of Dimes, 2015). Studies reflect this high rate in examining the components of distress by focusing primarily on maternal stress utilizing various operationalized definitions of stress. Studies focusing on depression or anxiety in

the development of a hypertensive disorder have received the least attention. Additionally, few studies have combined more than one component of psychological distress in the development of a hypertensive disorder.

The author carried out a systematic review of the literature from 2001 to 2016 to examine the associations of at least two components of psychological distress with the development of a hypertensive disorder in pregnancy. Furthermore, the author first operationally defined the concepts of maternal stress, anxiety, and depression and utilized a conceptual framework to guide this review.

Overview of Chapter Five

Pregnancies are characterized by psychological and biological changes. Psychological changes are often activated through hormonal fluctuations (Rallis, Skouteris, McCabe, & Milgrom). However, sometimes these changes are maladaptive and can lead to adverse outcomes such as in the development of a hypertensive disorder (Vianna et al., 2011). Prevalence of psychological distress has been reported in up to 25% of pregnancies (Çapik & Pasinlioglu, 2015). Limited research and lack of consensus about the association of psychological distress with the development of a hypertensive disorder prohibits the understanding of this relationship. Existing research has lacked using theoretical frameworks, has not been comprehensive by including all the components of maternal psychological distress and has lacked the use of valid measures to assess psychological distress. Furthermore, existing studies primarily have been cross-sectional and failed to capture changes in psychological distress over time.

The author conducted a secondary data analysis using data collected from a prospective multicenter study (Hieronymus, Combs, Coleman, Ashford, & Wiggins). A

case-control study was conducted. The cases, women with a hypertensive disorder of pregnancy, were frequency matched on age and parity with normotensive pregnant women. There were 29 women with hypertension and 87 without the disorder. Three hypotheses were tested using the PNI framework. In addition, valid self-report instruments evaluated maternal perceived stress as well as symptoms of depression and anxiety at two different time points during pregnancy. Results of this study did not support any differences in psychological distress between women with a hypertensive disorder of pregnancy and those without the disorder. Additionally, none of the psychological distress components, perceived stress, depressive symptoms, or symptoms of anxiety were independent predictors in the development of a hypertensive disorder. Body mass index was an independent predictor of this disorder.

Overview of Chapter Six

Chapter Six provides an overview of study findings and suggests recommendations for future research into the study variables of this dissertation as well as additional variables suggested by the comprehensive PNI framework. Further use of this framework is recommended to include interventional studies using coping strategies and modifying risk behaviors to reduce the psychological distress, inflammatory response and ultimately the adverse pregnancy outcome of a hypertensive disorder.

Chapter II: The Experience of Preeclampsia and Bed Rest: Mental Health Implications

Background

Preeclampsia is a major cause of maternal and fetal morbidity and mortality that affects 5-10% of pregnant women globally, 3-5% in the United States (U.S. Department of Health and Human Services, 2013). Women with preeclampsia experience significant physical as well as psychological hardship (Malakouti et al., 2015). Mental health issues, including stress and anxiety are often exhibited in this vulnerable population partly due to the rigid management of this high-risk condition including prolonged bed rest (Rubarth et al., 2012). Preeclampsia has recently been defined as new onset hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) and proteinuria (>300 mg/24 hr) after 20 weeks of gestation (Ramma, 2011). In the absence of proteinuria, new-onset hypertension with any of the following: thrombocytopenia (platelet count < 1000,000/microliter), impaired liver function, new development of renal insufficiency (elevated serum creatinine > 1.1 mg/dL), pulmonary edema, or new-onset cerebral or visual disturbances (American College of Obstetricians and Gynecologists, 2013). This new expanded definition of preeclampsia adopted in 2013 by the American Congress of Obstetricians and Gynecologists (ACOG) has increased the number of diagnoses by 20% (Woelkers, Barton, von Dadelszen, & Sibai, 2015).

Preeclampsia occurs primarily in first pregnancies and other risk factors include: chronic high blood pressure, chronic kidney disease, history of high blood pressure or preeclampsia in prior pregnancy, obesity, women younger than 20 years or older than 35 years, being African American, or having a family history of preeclampsia (U.S. Department of Health and Human Services, 2013). Each year in the United States, more

than 204,000 hospitalizations occur due to preeclampsia (Barton, Istwan, Rhea, Collins, & Stanziano, 2006). Serious maternal complications of preeclampsia can include acute renal failure, acute liver injury, seizures, pulmonary edema, hemolysis, and thrombocytopenia (Ramma, 2011). Since delivery of the fetus and placenta is the only relief of the syndrome, and fetal complications can arise with a preterm birth, interventions are often directed at preserving the pregnancy until closer to term.

Bed rest as a treatment modality for preeclampsia was first documented in the 1950s (Morris et al., 1957). In this landmark study, Morris et al. examined the impact of bed rest on blood pressure by comparing women on bed rest with women on bed rest performed leg exercises. Morris used these leg exercises to increase blood pressure simulating the increased blood pressure experienced with preeclampsia. Morris postulated that even in normal pregnant women, exercise decreases the perfusion to the uterus and possibly mimics the preeclamptic patient's circulation; thus suggesting a more profound decrease in uterine blood-flow in women experiencing preeclampsia (Morris et al., 1957). Because exercise diminishes circulation to vital organs it was thought that bed rest would improve circulation to these organs. This study was among the first to report that maternal bed rest reduced blood pressure and is thought to be the reason many healthcare providers began to recommend bed rest therapy for preeclampsia.
Healthcare providers continued to recommend bed rest as a treatment for the progression of preeclampsia. Historically, the reported benefits of bed rest were thought to include the reduction of edema, improved fetal growth, prevention of progression to severe preeclampsia, and improved outcomes for the pregnancy (Sibai, 1996). In 2012, ACOG created a task force to update and educate healthcare workers about the definition,

diagnosis, and management of preeclampsia and pregnancy-induced hypertension. The ACOG report resulting from this task force states that bed rest is no longer recommended as a primary prevention of preeclampsia and its complications, nor is bed rest recommended for the treatment of preeclampsia in most women (American College of Obstetricians and Gynecologists, 2013). However, bed rest is still being used in this population, as evidenced by the fact that 89% to 93% of both maternal fetal medicine physicians and obstetricians utilize bed rest for a variety of indications and in a variety of restrictions (Bigelow & Stone, 2011).

Data regarding the utility of holistic methods to address the mental health needs of high-risk mothers being placed on home or hospitalized bed rest is limited. In a randomized controlled trial (RCT) the efficacy of a single music session or recreation therapy intervention for hospitalized pregnant women effectively reduced antepartum-related distress (Bauer, Victorson, Rosenbloom, Barocas, & Silver, 2010). Yet another RCT using a holistic music therapy intervention (30 minutes on 3 consecutive days) was found be effective in reducing anxiety levels and improving physiological responses of pregnant women placed on bed rest (Yang et al., 2009). Support groups have also been found to be an effective method to assist high-risk mothers in coping with bed rest both in the hospital and at home (Adler & Zarchin, 2002; Maloni & Kutil, 2000). Maloni and Kutil reported an unstructured support group that provides hospitalized women on bed rest with an opportunity to voice their concerns in a supportive environment may be an important nursing intervention in helping these women cope (Maloni & Kutil, 2000). In the event women cannot be together physically, a virtual support group using the internet to reach women with high-risk pregnancies on home bed rest was shown to be effective.

Adler and Aarchin stated that women reported participating in the virtual focus group was valuable and beneficial in helping them cope with the difficulties of bed rest (Adler & Zarchin, 2002).

Preeclampsia is a serious condition with the potential for adverse outcomes, and although some investigators have described the perceptions, beliefs and emotional experiences of pregnant women with high-risk pregnancies who are placed on bed rest, fewer have researched preeclampsia, specifically or have revisited this topic since the 2013 release of the new ACOG guidelines. The psychological and emotional support these women may need has not been thoroughly documented and, holistic interventions have not been utilized to their potential. In order for clinicians to provide adequate psychosocial support to these women, it is important for us to gain a better understanding of the lived experience that women with preeclampsia have on bed rest and the effectiveness of the holistic interventions provided to these women.

Therefore, the primary aim of the study was to describe women's experience of having preeclampsia and being placed on extended bed rest during their pregnancy despite the newest recommendations from ACOG and bed rest for treatment of preeclampsia. Secondary aims included: 1. identifying key stressors that women experience while on bed rest, and 2. identifying healthcare provider management of maternal stress related to prolonged bed rest.

A qualitative descriptive approach provided a comprehensive summary of the experience of being placed on bed rest. According to Sandelowski (2000), qualitative description allows for 'low-inference' interpretation of the data that is likely to result in consensus among researchers. The primary component of qualitative descriptive

methodology entails using everyday language to describe participant's personal accounts providing a comprehensive summary of a specific phenomenon (Sandelowski, 2000). In qualitative description, data trustworthiness is established through the credibility, confirmability, transferability and dependability of the data.

Design and Method

Qualitative description was used to provide a comprehensive summary of the experience of being placed on extended bed rest and/or hospitalization for preeclampsia. ATLAS.ti 6.2 software was used to analyze the data. This software allows for analysis of qualitative data including interviews.

Recruitment and Sample

The study was approved by the Institutional Review Board at the University of Kentucky. In order to participate in the study, women had to meet these inclusion criteria: 18-45 years old, able to communicate in English, and have a current diagnosis or history of preeclampsia per self-report in the past ten years in which they were placed on some form of bed rest (home or hospital) for at least 7 days. Study participants were recruited through Facebook postings from Evidence Based Birth, a pregnancy and childbirth blog with more than 20,000 Facebook followers. After potential participants contacted the principal investigator, they were screened for eligibility and provided an email with a cover letter and link to Survey Monkey for informed consent. The minimum of a 7 day bed rest period was chosen based on previous selection criterion in studies completed by Gupton and Richter (Gupton, Heaman, & Ashcroft, 1997; Richter, Parkes, & Chaw-Kant, 2007). Women were excluded if they did not have access to a phone or computer.

In a four month time period, twenty women initially responded to the Facebook postings. Of the twenty women, seven women met inclusion criteria and completed the study. The remaining 13 women either did not meet inclusion criteria and/or choose to not enroll due to time constraints.

Data Collection

Following consent, the PI and participant established an interview date and time. Data were collected via a one-on-one recorded phone interview. Study participants were asked open-ended questions in an individual interview that took place over the phone. Guided questions were used to conduct the interview allowing for the participants to expand in any direction they chose. In addition to guided questions, a few perinatal questions such as gestational age at diagnosis, how bed rest was defined, how long ago since diagnosis and treatment, as well as some demographic information including: age, race, occupation, marital status, and number of children were obtained. See Appendix for interview questions. On average, the interviews lasted one hour, with a range of 37 minutes to 1 hour and 11 minutes. The activities of the PI and interview process were reviewed by two of the authors to demonstrate dependability with the research methods.

Data Analysis

Participants were de-identified and referred to as A, B, and C, etc. The recordings were professionally transcribed verbatim, and checked for accuracy. Following the design of Rubarth, et al (2012), transcriptions were read several times by the PI to achieve a basic understanding of the information and summarized. Three of the team members reviewed the transcripts and identified patterns. Once transcribed and verified, all voice recordings were deleted. Content analysis was used to analyze the data. The patterns

identified were coded and grouped into themes by three of the authors to decrease researcher bias and demonstrate confirmability reliability with the data. Codes were attached to the transcript to identify themes using ATLAS.ti 6.2. These were kept in a code book as a separate file. All meanings and themes were traceable back to the individual transcription to enhance credibility. The study of seven women with similar demographics did provide some level of richness for this group of women. This rich description of the experience of having preeclampsia and being placed on bed rest demonstrates transferability.

Results

The women of this study were all Caucasian with a mean age of just over 30 years old. They were all college educated, married, and employed full-time at the time of diagnosis. Two women were gravida 2, and the others were gravida 1. The length of bed rest was between 2 and 9 weeks for these women, and their gestational ages were between 29 and 37 weeks. See Appendix A for more demographic information and a bed rest timetable about the sample.

During data analysis, six themes emerged in which women described stressors that they experienced. These stressors included negative feelings and thoughts, lack of guidelines and/or knowledge about their diagnosis, lack of social support, not being heard, loss of normal pregnancy, and physical symptoms.

Negative feelings and thoughts

All of the participants described having negative feelings and thoughts related to their experience of preeclampsia and being placed on bed rest. Some of these negative feelings could be characterized as anxiety related symptoms. The participants used terms

like “nervous wreck,” “major meltdown,” “stressed out,” and “scared” to describe their mood. One participant recalled having this anxious thought after she “Googled” preeclampsia:

“I saw what could go wrong and then it was like, ‘Oh my gosh, I’m going to die and my baby is going to die,’ and it all started spiraling out of control.”

And another woman stated:

“Every time I went to the doctor I had this like near anxiety attack.”

Women shared the negative thoughts that occurred to them while they were on bed rest:

“To me it felt like I was just sitting on bed rest, waiting to have a seizure, you know, waiting to completely start circling the drain.”

Some women experienced more depression-like symptoms of “mental funk” and used words like “sad and frustrated” to describe how they felt. One woman talked about a friend who committed suicide shortly after having a complicated pregnancy and delivery. She expressed concern and empathy toward her friend saying:

“I just sometimes wonder and I can almost feel where it would be easy to fall into that because you have all these negative feelings anyway.”

Another woman shared:

“I was a wreck. I probably cried every day.”

In addition to anxiety and depressive symptoms, five of the seven women revealed fearful thoughts they had about their unborn child:

“It was a very strong mental feeling of something is not right and this pregnancy needs to end…I felt an impending doom…I felt like I was being poisoned, like the baby

in my body was killing me slowly." Another woman stated, "When you start reading about growth restriction, it's very scary."

Finally, women mentioned experiencing negative thoughts about failure, guilt, and loss. Four of the seven women described these types of negative thoughts about their bodies and pregnancies. One woman noted:

"I feel like a failure. I feel like I am flunking, you know, like this is my fault. That's how I felt about these blood pressures."

And another stated:

"My caregivers from the beginning were telling me to make sure you're exercising, make sure you are eating a certain way and it will help to make sure you don't get complications…I was kind of mad because I was following the recommendations and they didn't work. I felt like I did all of this for nothing."

Still another commented:

"I wanted to be pregnant. I'm not really ill, I should be stronger and I should be handling this better."

Lack of guidelines

Frustration was a common feeling from four of the seven women when dealing with their healthcare providers throughout their complicated pregnancies. These women often received conflicting information or "mixed messages" from various providers of a group, or did not receive any information pertaining to their diagnoses. Often not having continuity of care led to miscommunications or inconsistent information being provided to these women. Only two of the seven women could positively identify a standard

protocol for preeclampsia being used during their pregnancies. One woman was especially frustrated with her providers stating:

"I would go in and say I need to have a non-stress test and it was never on the schedule. One doctor wants me there twice a week, then I end up seeing his partner and he says I don't need to come twice a week but only once a week. Then I get stuck with the other doctor and he asks why did I not come in twice a week for my stress test?"

The same woman goes on to say:

"I went in to the office because I gained 7 pounds in 3 days and my blood pressure is teetering over that 140/90 range so I expected to be induced…a different doctor sees me and she says I'm fine and not even preeclamptic…Don't come back unless you are consistently 140/90"

Another woman tells the story of how she was induced stating:

"I went in for my non-stress test, my blood pressure was 150/110 and the midwife said, we'll keep that plan of not inducing for another five days and then went out, talked to the OB, and came back in and said, no, we're inducing you right now."

Some women experienced a feeling of having a general lack of information about their diagnosis. Four of the seven women mentioned that they specifically wanted their care providers to use evidence-based medicine, but they were not provided with information about the evidence behind their care, and they sometimes doubted the information given to them by their providers. One woman is still doubtful that she had preeclampsia at all during her pregnancy. She states:

(Her provider tells her) "You know you're developing preeclampsia. I said oh really, how do you know? He said your uric acid is five…and it should go down at the

end of pregnancy. I knew this isn't true and I made it my mission to find out what the normal levels of uric acid at the end of pregnancy and sure enough, it goes up until you deliver."

And

"I tried to do everything they (the perinatology office) said to do, which was to stop exercising and bed rest and all of that stuff, even though at the back of my mind I pulled up the ACOG recommendations that said no one should be on bed rest anymore."

Lack of social support

All seven of these women expressed a need for increased social support during this time of their pregnancy. They used words like "need" and "would have helped." One woman mentions how she tried to reach out to her church but they couldn't see her need. She states:

"My preacher is a women and I texted her and told her I was on bed rest. I was shocked that they weren't asking if they could send someone over with a meal or whatever. Not to judge my church, I was just kind of shocked by that because I feel like if someone is older or something, everyone jumps to help them."

Three of the women did not feel support from their health care providers. One woman did not feel she had any sort of relationship with her providers, and another felt she could not call her provider's office with questions or concerns. The third woman described an unsupportive encounter at her provider's office:

"At the perinatology office, the nurse that checked me in said, like she made this horrible face one day and said 'oh, that blood pressure is just terrible'. Those were her exact words."

These women often relied on their spouses and family for support, but they worried about the stress placed on their families as well. Some of these women noticed the toll their condition was taking on their spouses and family members. Four of the seven women mentioned the added stress they noticed particularly in their spouses. They mentioned "hard", or "extremely stressful", or "absolutely stressed" when describing the impact their situation was having on their husbands. One woman states:

"He knew I was sick and he knew I was not feeling well. I think that just scared him in general because he's a worry wart about health-type things."

Another woman mentions:

"I think that he did his best to not (be stressed). He's king of an easygoing guy and I think he did his best to be optimistic about it, but it was definitely stressful for him."

Not being heard

One of the most common stressors, identified by six of the seven women in this study, was a feeling of not being heard by their providers. All of these women had college educations and tried to communicate with their providers, but they felt that their questions were not answered and their concerns were not addressed. They used phrases like "blown off", "no consideration", "brushed off", and "write everything off" when discussing how they felt when they addressed concerns they had with their providers. A woman tells of her provider's response to her questions stating:

"When I had questions, she would just say oh that's normal, everyone does that, without even answering the question. Even to the point where I suggested that we don't

try medicine first. She just kind of laughed at me and said, you let me know how that goes."

Yet another woman explained that she felt her providers thought she was a hypochondriac.

"Some of them just want to blow me off and like: This girl is crazy. She comes in and brings her blood pressure and says she needs a non-stress test and all this stuff."

One woman went as far as bringing in proof of her physical symptoms to try to gain some attention from her providers saying:

"I started to feel really bad and I started to feel like there was going to be a problem and every time I brought this up, you know I even took pictures of my legs at the end of the day and I showed it to them and it was just like, oh every pregnant woman swells, and gets short of breath."

Loss of normal pregnancy

Four of the seven women discussed what they perceived as a loss. Each of these women had an idea in their head about their pregnancies and struggled to manage their feelings when their pregnancies no longer "fit" their idea of normal. One women had developed a birth plan and found out that:

"You have what your actual pregnancy is, which is none of the ways you anticipate planning."

Another woman described her birth plan as a picture stating:

"It's very hard to take that picture you have and repaint it."

One woman describes the transition of a normal pregnancy to one with preeclampsia as this:

"It went from totally healthy and normal and we're going to have a baby to not feeling healthy and seeing that my body didn't like being pregnant."

Physical symptoms

The most common physical symptom of these women was fatigue. The women used words like "tired", "exhaustion", and "lack of ambition". One woman mentioned:

"Even if I wasn't sleeping, I found that I didn't have a lot of energy doing things."

One woman recalls her swelling being so bad that it caused "a lot of carpal tunnel" and her husband had to "lift up her foot high enough to put on underwear."

Another woman describes and overall feeling of sickness or flu-ish stating:

"I guess you know that kind of punky, headachy, nothing quite feels right (feeling)".

Discussion

There is limited research regarding the experience of women on bed rest for the prevention or treatment of preeclampsia specifically, rather they focused on bed-rest for high-risk pregnancies in general. Some studies reported on the experience of bed rest either at home or in the hospital. Women with preeclampsia may already be experiencing increased anxiety, fear, and stress, which could be aggravated by early maternal bed rest or hospitalization prior to delivery (Souza et al., 2007). Schroeder reported that women with a high-risk pregnancy, such as preeclampsia, described a high level of physical, emotional, familial, and economic hardship when placed on bed rest (Schroeder, 1996). Gupton et al. also examined high-risk pregnant women on bed rest and determined these women identified stressors, including lack of control, assuming a sick role, concerns for fetus, missing out, and boredom (Gupton et al., 1997). May described women's stressors

as manageable if they could balance the needs of family with activity restriction, but those that could not find balance experienced uncomfortable levels of emotional distress (May, 2001). Leichtentritt, et al., described the experience of hospitalized women with high-risk pregnancies as having an essential theme of ambivalence, that is to say, they feel anxious about the situation, but hopeful of the outcome; they feel emotionally "in" but physically "out" of their houses (Leichtentritt, Blumenthal, Elyassi, & Rotmensch, 2005). Richter, et al., also reported on high-risk hospitalized women having stressors related to feelings of loss of control and being a burden (Richter et al., 2007). Rubarth, et al., described women hospitalized with high-risk pregnancies as experiencing a "war within" as they battled an emotional roller coaster and feelings of imprisonment (Rubarth et al., 2012).

The primary aim of this study was to describe the experiences these women have with preeclampsia and subsequent bed rest. Almost 20 years later, the experiences of these women are similar to those from the past, including this core set of feelings associated with a high-risk pregnancy such as preeclampsia and being placed on bed rest. One secondary aim included identifying the stressors these women experience. Many stressors are associated with having a diagnosis of preeclampsia and subsequently being placed on bed rest. The three primary stressors for these women included negative feelings including symptoms of anxiety and depression, frustration with the lack of evidence-based practices from health care professionals, and a feeling of not being heard by the health care professionals.

The women of this study were frustrated with the apparent lack of evidence-based guidelines being used by their providers. Complete bed rest has been questioned since the

early 90's due to the potential complications of maternal orthostatic hypotension, depression, venous thromboembolism, muscle atrophy, and bone demineralization (Schroeder, 1996). In addition, there is a psychological toll many women experience while placed on bed rest. Some researchers have stated that is not only complete bed rest a non-evidence-based practice, but that it is also an unethical treatment for pregnancy (McCall, Grimes, & Lyerly, 2013). In the 2013 report from the American College of Obstetricians and Gynecologists, experts suggested that bed rest or the restriction of other physical activity should not be prescribed for women with preeclampsia without severe features (American College of Obstetricians and Gynecologists, 2013). Additionally, bed rest is not defined the same within the maternal-fetal health community. All seven of the women in this study were given different definitions of bed rest and what bed rest entailed. Some women were told modified meant being in a bed or recliner unless using the bathroom while for others, it meant no exercise or work, or some activity for an hour or so occasionally. Nonetheless, varied types of bed rest are commonly prescribed for women with preeclampsia regardless of the severity.

In our study, four of seven women were actively educating themselves about preeclampsia, the risks involved, and the treatments recommended or not recommended. These women wanted to be actively participating and engaged in their own care. Our finding is similar to research reported by Harrison et al, who found that most women wanted to be active participants in the decision making process around their care. Active participation was defined as having access to information about choices, and partnering with your healthcare provider to make decisions about pregnancy (Harrison, Kushner, Benzies, Rempel, & Kimak, 2003). One woman in our study had accessed the ACOG

guidelines and knew that bed rest was no longer recommended, and yet her provider placed her on bed rest anyways. She did not feel she could say anything to her provider about the contradiction, and she felt conflicted and frustrated with her provider. In the Harrison et al. study, women reported being dissatisfied when they felt left out of decision making, and were unable to ask for clarification of what was heard discussed about their care among their providers (Harrison et al., 2003).

Today, women have more on-line access to information regarding treatment options for preeclampsia. Most women obtain at least some portion of prenatal health information through the internet (Huberty, Dinkel, Beets, & Coleman, 2013; Lagan, Sinclair, & George Kernohan, 2010). Providers should be aware that many women are taking an active role by seeking out information regarding their pregnancies. By talking with women about what information they are reading online about their condition, this could reduce the frustration experienced by these women.

Furthermore, their feelings are still not being addressed effectively by the healthcare system. The women included in this study experienced the same feelings and many also stated these feelings were not addressed by their providers. Another secondary aim was to learn what approaches providers used to address the stressors these women experience. Overall participants felt that their feelings were not addressed rather dismissed by their providers as six of the seven described feelings of being "blown-off" or "brushed-off". They felt that many of their questions went unanswered. Other studies have shown similar findings. In a study by East, et al., 19% of the women felt that doctors and midwives did not believe the mother was unwell when their preeclampsia became more severe (East, Conway, Pollock, Frawley, & Brennecke, 2011). The feeling

of not being heard affects how women view their prenatal care. Six of the women of this study did not reflect a positive relationship with their providers when they were not listened to or perceived as an over-concerned client. Women weigh certain characteristics in satisfactory prenatal care, one of which is questions to be asked and questions be answered along with understanding their personal experiences (Harrison et al., 2003). The fact that women in our study felt dismissed or not heard by their providers could raise serious safety issues as well, because the women might not be heard—or may be less likely to speak up—if they experience severe symptoms or warning signs related to their preeclampsia.

Six of seven women explained how their providers never asked them how they felt throughout their high-risk pregnancies or what their feelings were about being placed on bed rest. When the women were asked how they would have responded if their providers had asked about their psychological well being, they claimed they would have been open and honest. Not surprisingly, these women wanted their providers to address their concerns. Results from a study by Harrison et al. support our findings, as women in their study reported that they wanted to be asked questions (from their providers) about their medical and emotional status (Harrison et al., 2003).

Clinical and Nursing Implications

The stressors perceived by the women of this study are similar to those reported in previous research conducted nearly 20 years ago. These women reported significant mental health issues such as stress, anxiety and frustration. These feelings may be initiated or exacerbated by several factors such as having a high-risk pregnancy, knowing that evidence-based practices are not being utilized, and feeling they are not heard by

their providers. Although the women in this study were all Caucasian living in the United States, the recommendations from this study could be applied to women around the world. Screening women for psychological stress and offering holistic options to help manage stress could lead to healthier pregnancies for these women. During a pregnancy, women encounter a variety of healthcare professionals including nurses, doctors, and midwives. Any of them could address some of these factors by first exploring the feelings that women are experiencing with their high-risk pregnancy. Often nurses are the first responders when these women have complaints or concerns. Nurses could utilize that contact to explore the needs of these women. Tools such as the Everyday Stressors Index (ESI) (Hall, Williams, & Greenberg, 1985) and Generalized Anxiety Tool (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006) can provide a measure of the perceived stress and anxiety these women are experiencing. Exploring what type of involvement each client is comfortable with, whether active or passive, and partnering with the client in decision-making, could offer the client a more satisfactory experience. Health care professionals should talk with their clients about evidence-based practices, and directly ask and encourage open communication with their clients about what they know about their high-risk pregnancy. These techniques may help alleviate misinformation or confusion on the part of the client. Finally, health care professionals should adopt a more holistic and individualized approach to manage women experiencing preeclampsia. Such an approach should incorporate a psychosocial wellness screening to assess for knowledge about the disease while carefully listening to individualized concerns. Techniques such as music therapy and focus groups, both in person and on-line, have promising results in helping women cope with the stressors of being placed on bed rest

with a high-risk pregnancy (Adler & Zarchin, 2002; Bauer et al., 2010; Maloni & Kutil, 2000; Yang et al., 2009).

Implications for Future Research

Future research should focus on stress reduction strategies specific to women experiencing prolonged bed rest due to preeclampsia. Over the past two decades, the primary stressors associated with preeclampsia and bed rest (anxiety and frustration) have not changed (Schroeder, 1996). Interventional research focused on improving psychosocial wellness during this critical time period is warranted. Further, as healthcare delivery and management of high-risk pregnancy continues to evolve, future studies should be directed at implementation and evaluation of novel evidence-based practices, with particular focus on how these practices are communicated to the client. Improved communication, including teach-back methodologies, may provide to be beneficial in reducing maternal stress and anxiety while on prolonged bed rest.

Study Limitations

This study utilized qualitative methods, and there was a lack of demographic differences; thus data are not generalizable. Further, women for this study were purposively chosen through the Evidence Based Birth® website; thus indicating a potential selection bias as these women were actively seeking information to educate themselves. However, this could also be described as strength, as the authors were able to take an in-depth look at the experience of women with preeclampsia on bed rest who wanted to be active participants in their care, and are motivated to learn about evidence-based practices for preeclampsia. Although there were only seven participants, the in-depth qualitative interviews allowed for a rich description of having preeclampsia and

experiencing prolonged bed rest. Future research should include expanded recruitment (non-online) to ensure a more diverse sample. The data was collected through self-reporting of these women, including a diagnosis of preeclampsia. This can be considered a weakness, but these were their stories. The authors recognize that recounted experiences are filtered through the interviewee's memory and in one case that memory was 10 years ago, but these women recounted their stories in great, colorful detail that the authors tried to capture

Conclusions

This study provides researchers and health care workers with a current viewpoint of the experience of women with preeclampsia placed on bed rest, and hopefully will lead to a better understanding of their needs. Preeclampsia and bed rest are associated with persistent stressors, including frustration, depression, and anxiety, that are often overlooked by health care providers. Further, women report increased stress when providers' practices and recommendations conflict with evidence-based practices, and feelings of being dismissed by their providers during the course of their high-risk pregnancy. Care for these women can be improved if health care providers assess and manage psychosocial wellness, consistently follow evidence-based practices, and ensure time for effective communication and mutual exchange of information.

Chapter III: The Association of Maternal Stress and Immune Response with Development of a Hypertensive Disorder

Introduction and Purpose

Hypertensive disorders in pregnancy are common complications occurring in 5-10% of all pregnancies in the United States (Kuklina et al., 2009). This high risk complication is associated with increased maternal and fetal morbidity and mortality, and is a risk factor for the development of maternal cardiovascular disease later in life (Eiland et al., 2012). In the United States, the rate of pregnancy-related mortality from hypertensive disorders in 2012 was 7.6% (Centers for Disease Control and Prevention, 2016). Preeclampsia is the most prevalent hypertensive disease of pregnancy (Pennington, Schlitt, Jackson, Schulz, & Schust, 2012), with 17% of patients with gestational hypertension developing preeclampsia (Lo, Mission, & Caughey, 2013).

Although the exact mechanisms underlying preeclampsia remain unclear, there is evidence of the involvement of a maladaptive maternal inflammatory response. Systemic inflammation is common to all pregnancies but it has been proposed that preeclampsia results from an imbalance in this response (Ramma, 2011). Researchers have demonstrated an association between inflammation and the endothelial dysfunction linked with preeclampsia, more specifically an increased pro-inflammatory response. Figure 3.1 is a theoretical framework developed by Lazdam et al. in 2011 illustrating the inflammatory response and its relationship to endothelial dysfunction (Lazdam et al., 2011).

One of the factors that may adversely influence the inflammatory response is maternal perceived stress. Psychological stress may increase the risk for preeclampsia by increasing activation of the maternal inflammatory system (Christian, 2012b; Coussons-

Read et al., 2003; Crosson, 2012; Zhang et al., 2013). Limited data exist measuring these phenomena at each trimester during pregnancy. Substantial changes occur in maternal immune function over the course of a pregnancy; therefore, understanding the inflammatory process over each trimester would be beneficial (Christian, 2012b). The purpose of this study was to explore the association of maternal stress and inflammatory response with development of preeclampsia or other hypertensive disorder during pregnancy. The author tested the following specific aims: 1) determine differences in serum cytokine levels (IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNFα) at each trimester of pregnancy based on maternal perceived stress (Everyday Stressor Index) categorized as high or low in women who do and do not develop a hypertensive disorder; 2) To determine the differences in serum cytokine levels over each trimester between stress scores (high or low) and a hypertensive disorder (hypertensive or normotensive).

Background

Preeclampsia is a severe complication of pregnancy affecting 5-10% of pregnant women globally and 3-5% in the United States (U.S. Department of Health and Human Services) (Ananth, Keyes, & Wapner, 2013; Lo et al., 2013). From 1980 to 2010, the prevalence of all cases of preeclampsia in the U.S. increased from 3.4% to 3.8%; however, the rate of severe preeclampsia increased by more than three-fold during this time from 0.3% to 1.4% (Ananth et al., 2013). Preeclampsia is one of the primary causes of maternal morbidity and mortality. Globally 50,000 women die each year from preeclampsia (Duley, 2009). Maternal morbidity associated with severe preeclampsia

includes acute renal failure, acute liver injury, seizures, pulmonary edema, hemolysis, and thrombocytopenia (Ramma, 2011).

In addition, preeclampsia is a major cause of fetal mortality and morbidity. Researchers reported a stillbirth rate from 9 in 1000 to as much as 21 in 1000 related to mild and severe preeclampsia respectively (Simpson, 2002). Fetal morbidity associated with preeclampsia is also related to preterm birth, intrauterine growth restriction, fetal weight, and Apgar scores (Can et al., 2011; Mihu, Razvan, Malutan, & Mihaela, 2015).

Hypertension during pregnancy is categorized as chronic hypertension, gestational hypertension, preeclampsia (including mild, superimposed, and severe forms), and eclampsia. Preeclampsia is defined as the new onset of hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and proteinuria (≥ 300 mg/24 h) after 20 weeks of gestation. Severe preeclampsia is defined by systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg and proteinuria ≥ 2 g/24 h (American College of Obstetricians and Gynecologists, 2013). In the absence of proteinuria, preeclampsia can be diagnosed as hypertension in association with thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new visual disturbances (American College of Obstetricians and Gynecologists, 2013). Preeclampsia can be categorized as early onset (< 34 weeks gestation), and late onset (> 34 weeks gestation) (Eastabrook, Brown, & Sargent, 2011).

The severity of the disease, gestational age at time of disease onset, and the existence of comorbidities affect the pregnancy outcomes. Women who develop the disease after 36 weeks gestation are less likely to experience adverse outcomes than women who develop the disorder before 33 weeks gestation primarily due to longer

gestation (Sibai, Gus; Kupferminc, Michael, 2005). For example, both gestational age (39.1 weeks) and birth weight at delivery (3217 grams) are higher in pregnancies with a preeclampsia diagnosis after 36 weeks (Sibai, Gus; Kupferminc, Michael, 2005). Additionally, rate of fetal death was approximately six times higher (AOR, 5.8; 95% CI, 4.0-8.3) among women with early onset of the disease (Lisonkova & Joseph, 2013).

Preeclampsia can also have long-term maternal effects. A history of preeclampsia is associated with doubling the maternal risk factor for developing cardiac, cerebrovascular, and peripheral vascular disease compared to women without this risk factor (Eiland et al., 2012; Giguère et al., 2012; Gilbert et al., 2008). In addition, women with a history of preeclampsia have a 3-5 fold increased prevalence of developing metabolic syndrome later in life (Giguère et al., 2012).

Normal pregnancy results in changes in maternal physiology including changes in host response. A shift toward an anti-inflammatory response and inhibition of a pro-inflammatory response is associated in normal pregnancy (Ramma, 2011). Pro-inflammatory markers include tumor necrosis factor alpha, interleukins -1α, -1β, -2, -6, -8, and -12. Anti-inflammatory marker includes interleukin-10 (Moreli et al., 2012; Ramma, 2011). Preeclampsia is hypothesized to be due to a maladaptive maternal immune response to pregnancy, specifically exaggerated inflammation (Eiland et al., 2012; Palm et al., 2013; Ramma, 2011).

Preeclampsia is associated with an overall pro-inflammatory systemic environment with elevated amounts of pro-inflammatory cytokines (Szarka et al., 2010). Tumor necrosis factor alpha (TNFα) increased in the second and third trimesters in women with preeclampsia (Moreli et al., 2012; Palm et al., 2013; Szarka et al., 2010).

Cytokines interleukins IL-6 and IL-8 increased, while IL-10 decreased when measured in the third trimester or at diagnosis (Borekci, Aksoy, Al, Demircan, & Kadanali, 2007; Kronborg et al., 2011; Szarka et al., 2010). Serum biomarker levels provide quantifiable measures of this inflammatory response; however, few studies were longitudinal in design. Exploring these changes throughout pregnancy, and prior to the development of preeclampsia holds promise in early identification and intervention for at-risk women.

Heightened, perceived maternal stress experienced during pregnancy can increase the risk for preeclampsia. Physiological responses occur in the body when exposed to stress (Crosson, 2012). These responses include the release of various inflammatory markers (Coussons-Read et al., 2007) and stress hormones such as cortisol (Crosson, 2012). Coussons-Read et al. proposed the hypothesis that maternal perceived stress during the prenatal period has a negative effect on pregnancy outcomes by altering the maternal immune response (Coussons-Read et al., 2003). Perceived stress in the mother's life during pregnancy was associated with an increased risk (odds ratio (OR), 1.7%; 95% CI, 1.3-2.2) of preeclampsia (Yu et al., 2013). Women with perceived stress were more than twice as likely to develop preeclampsia during their pregnancy (OR, 2.1; 95% CI, 1.5-2.8; $p<0.001$) (Zhang et al., 2013). Elevated maternal perceived stress was also related to higher levels of IL-6 early and late in pregnancy, and lower levels of IL-10 early in pregnancy (Coussons-Read et al., 2007). Unfortunately, biomarker measures are not consistent across studies and the conclusions about their importance equivocal.

There are limited data about maternal stress and inflammatory response measured at each trimester, and the association with the development of preeclampsia. Determining maternal stress levels in conjunction with measurement of trimester-specific immune

markers may assist practitioners in identifying women at risk for the development of preeclampsia. Given the relationship between trimester-specific maternal stress and inflammatory response is established, early detection of preeclampsia may be possible; thus increasing likelihood of improved pregnancy outcomes.

Design and Method

The current investigation was a secondary analysis of a longitudinal, repeated measures, multicenter study of culturally and ethnically diverse pregnant women (Ashford et al., 2015). The primary aim of the parent study was to determine if trimester-specific prenatal inflammatory markers linked with psychosocial and biobehavioral variables pose a significant risk for preterm birth. The parent study was conducted at the University of Kentucky College of Nursing from 2010-2014 and was approved by the University of Kentucky's Institutional Review Board (IRB). In the current study, a 1:2 case control design from data collected in the parent study was used. Participants were matched on age and parity. Cases consisted of women diagnosed with a hypertensive disorder of pregnancy, while controls consisted of women without a hypertensive disorder.

Sample

The inclusion criteria for the parent study were pregnant women older than 16 years of age with a singleton gestation. The exclusion criteria for the parent study were history of Type 1 or Type 2 diabetes, history of any heart disease, current history of illegal or prescription drug abuse via urine drug screen, diagnosis of bacterial vaginosis or sexually transmitted disease, any autoimmune disease, and multifetal pregnancies. Women with chronic disease and/or multifetal pregnancy were excluded due to their

significant association with preterm birth (Institute of Medicine, 2006). Other exclusion criteria were based on factors that would alter the maternal immune response and/or were an independent risk factor for preterm birth. For this analysis, inclusion criteria were the same as the parent study with the exception that participants were selected from the sample if they had a hypertensive disorder.

Setting

Three prenatal clinics in Kentucky and Virginia served as recruitment sites in the parent study. Four prenatal office visits served as collection periods: 1) 5-13 weeks; 2) 14-26 weeks; 3) 27-36 weeks gestation, and 4) 2-8 weeks postpartum. At least four weeks were allotted between collection points. Enrolled subjects provided demographic information and reproductive history. Serum samples for the parent study were obtained at each collection point during routine prenatal visits.

Measures

In the parent study, serum samples were collected using standard venipuncture. For long-term storage, blood samples were centrifuged, pipetted into aliquots, and stored at – 80^{o} c. Samples were slowly thawed prior to analysis. Cytokine samples were analyzed undiluted. All samples were run in duplicate according to manufacturers' protocols (Ashford et al., 2015).

Systemic inflammation. Systemic inflammation was defined as a response from immune-related cells resulting in the release of inflammatory cytokines. A mild maternal response is considered normal in pregnancy (Redman & Sargent, 2004). We measured systemic inflammation through serum inflammatory biomarkers, specifically pro-inflammatory cytokines interleukin1α (IL-1α), interleukin 1β (IL-1β), interleukin 6 (IL-

6), interleukin 8 (IL-8), tumor necrosis factor α (TNFα) and anti-inflammatory interleukin 10 (IL-10) using the Luminex system.

The Luminex system is a highly reproducible and reliable bead-based assay that enables quantification of multiple proteins simultaneously (Tighe, Negm, Todd, & Fairclough, 2013). The Luminex multiplex bead assay has become an important tool for detecting and measuring cytokines due to its ability to measure multiple cytokines simultaneously with a small sample size that was not previously possible with older technologies (Khalifian, Raimondi, & Brandacher, 2015). When compared to the gold standard of cytokine measurement enzyme-linked immunosorbent assay (ELISA), the multiplex bead array has a high correlation coefficient ranging from 0.912 – 1.0 (Elshal & McCoy, 2006).

In addition, we collected questionnaire data for several psychosocial variables including perceived stress. This data were collected immediately following biomarker collection at each time point by trained staff. Questionnaires were given to study participants to complete on their own during their office visit. Staff provided verbal instructions on how to complete the surveys. Questionnaires were administered via a web-based survey or paper copy according to their preference. All written material was available in English and Spanish at a 6th grade reading level. Participants received a $20 gift card after each collection point as an incentive. Women were free to withdraw at any time during the parent study.

Prenatal Stress. Stress was defined as the maternal psychological stress perceived during pregnancy and measured through the Everyday Stressors Index (ESI) Hall (1983). The ESI (Hall, et al., 1983) is a 20-item self-report questionnaire used to evaluate

perceived stress during perinatal period. ESI consists of a 4-point Likert scale ranging from "not at all bothered" to "bothered a great deal"; total scores range from 0-60 with higher scores indicating a higher level of stress (Hall et al., 1985). The index assesses five common sources of maternal stress such as role overload, financial concerns, parenting worries, employment problems, and interpersonal conflicts. The participant reflected the number of times an event occurred in their life within the previous year and selected the appropriate response. A cumulative score is obtained by summing each item. The instrument was developed to measure individual responses to common stressors faced by low-income mothers with young children. In samples of mothers of young children, the ESI demonstrated strong internal consistency with alphas ranging from 0.81 to 0.86 (Hall & Farel, 1988; Hall, Kotch, Browne, & Rayens, 1996; Hall et al., 1985; Peden, Rayens, Hall, & Grant, 2004). Content and construct validity of the ESI were also supported in a number of studies (Hall, 1983; Hall et al., 1996; Pollock, Amankwaa, & Amankwaa, 2005). The majority of participants recruited in the parent study fit the low-income demographic with 66% insured through Medicaid.

Demographic characteristics. Age, race (Caucasian vs. Non-Caucasian), parity, marital status, income level, and education level were collected. Demographic data were collected through self-report at the first trimester appointment.

Procedures

An exemption certification was not required, as the parent study had been closed. Cases and controls were frequency matched on age (5 year increments) and parity (yes or no) in the same trimester of pregnancy with a 2:1 control to cases ratio. Controls were randomly selected normotensive women from the study population based on selected

matching described above. Cases involved women who developed a hypertensive disorder via medical record during pregnancy. Frequencies were run to determine any missing data. Since this a secondary data analysis, missing data was filtered out prior to analyses. Race, income level, marital status, and education level was all recoded into smaller groups due to sample sizes. The data were markedly skewed. Therefore, inflammatory markers were successfully transformed by taking the natural log prior to analysis. However, perceived stress score (ESI) could not be successfully transformed after numerous attempts so it was categorized into high stress (above 75th percentile) and low stress (below 75th percentile) using a cut point of 3.

Data Analysis

Preliminary analyses included descriptive statistics to characterize the participants in the secondary analysis. Independent t-tests and chi-square tests were used to compare study variables between women with a hypertensive disorder (cases) and those without (controls). Independent t-tests were used to determine if there were differences in serum inflammatory biomarker levels between women with a hypertensive disorder and women without the disorder measured in each trimester. There were 21 women with a hypertensive disorder and 42 women without a hypertensive disorder with data for each trimester used in this analysis. To address the first aim, independent t-tests with an ESI score cut-point of 3 (75th percentile) were used to determine if there are differences in serum levels of inflammatory biomarkers based on categorized high and low stress in each trimester between women who develop a hypertensive disorder and those who do not.

To address specific aim #2, repeated measures mixed modeling was used to discern differences in inflammatory biomarker levels by stress level and hypertension status during pregnancy, using the MIXED procedure in SAS. The between subject factors for each mixed model included stress level (high/low) and having a hypertensive disorder (yes/no) during pregnancy. Each model contained these main effects and the main effect of time (trimester), as well as their interactions. In the initial models (one for each cytokine), the interaction among stress level, hypertension status, and time was tested but removed from each model due to lack of statistical significance. Thus the final model for each cytokine contains the main effects and two-way interaction terms. Post-hoc pairwise comparisons for significant main or interaction effects were accomplished using Fisher's Least Significant Difference procedure. All analysis was conducted with SPSS v. 22 and SAS v. 9.4. A priori statistical significance was $p \leq .05$.

Results

Patient Characteristics

Participants included in the analysis were 1st trimester hypertensive (n=33) and non-hypertensive (n=64), 2nd trimester hypertensive (n=31) and non-hypertensive (n=62), and 3rd trimester hypertensive (n=28) and non-hypertensive (n=56). Table 3.1 illustrates the sociodemographic characteristics and baseline stress scores for this sample (n = 97). Per design, this sample consisted of 33 (34%) pregnant women with a hypertensive disorder and 64 (66%) without the disorder. The average age for the group was 26 years old. The majority of the samples were Caucasian (75%). The majority held greater than a high school education (79%). The majority 78% were married or living with a partner while 22% of participants were single or not living with a partner. There

was a significant difference in marital status between the two groups. More of the sample 57% had an income greater than $30,000 with the remaining 43% had an income below $30,000. There were no differences in baseline stress scores between hypertensive and normotensive women in this study.

Table 3.2 illustrates the average levels of IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNF-α and p-values for the subgroup (n = 63) with inflammatory biomarker data in each trimester of pregnancy divided by development of a hypertensive disorder or not. There were no significant differences in serum levels of these inflammatory biomarkers between these two groups in any of the three time points.

Specific Aim 1

Table 3.3 illustrates the average levels of IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNF-α and p-values for the non-hypertensive group based on high and low stress. There were significant differences in the third trimester in serum levels of IL-1β, IL-10, and TNF-α with lower levels in the high stress group. Table 3.4 illustrates the average levels of IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNF-α and p-values for the hypertensive group based on high and low stress. There were significant differences in serum IL-6 in all three trimesters with the high-stress group having higher levels. Additionally, IL-8 was significantly higher for the high stress group in both second and third trimesters. Finally IL-1α was significantly higher for the high stress group in the third trimester.

Specific Aim 2

Serum levels across trimesters by stress level

Repeated measures models showed significant main effects of stress level (high/low) and hypertension status for IL-8 (see Table 3.5). For the inflammatory

biomarker with significant stress level main effect, the levels were reduced in those with high stress compared to women with low stress. No differences were detected in IL-1α, IL-1β, IL-6, IL-10, or TNF-α by stress level, and the interaction between trimester and stress level was not significant for these inflammatory biomarkers with the exception of IL-1α.

There was a significant difference in the change of serum IL1- α levels across pregnancy between women with high stress and low stress (i.e., significant stress level by trimester interaction effect; see Table 3.5). Women with high stress had lower levels of IL1-α in the first trimester compared to women with low stress; there were no differences between the groups in mid to late trimesters.

Serum levels across trimesters by stress level and hypertension status

Repeated measures models showed a significant difference in the change of serum IL-10 levels across pregnancy between women with high stress and a hypertensive disorder compared to normotensive women with low stress (i.e., significant stress level and hypertension status by trimester interaction effect; see Table 3.5). Serum levels of IL-10 were significantly higher in the third trimester in women with high stress and a hypertensive disorder compared to normotensive women with low stress levels. There were no differences detected in the serum IL-1α, IL-1β, IL-6, IL-8, and TNF-α levels and the interaction between trimester, stress level, and hypertension status.

The main effect of trimester, regardless of stress level or hypertension status, was not significant for any of the serum inflammatory biomarker measurements. This subsample consisted of 63 women whose stress scores were available for all three trimesters.

Discussion

In the present study there were no differences in serum levels of IL-1α, IL-1β, IL-6, IL-8, IL-10, or TNF-α between women who developed a hypertensive disorder and women who did not develop the disorder. Our findings are contrary to those of other researchers who found levels of TNF-α were higher in the third trimester for women with a hypertensive disorder (Ramma, 2011; Szarka et al., 2010). Increased levels of IL-6 during the last trimester in hypertensive women have been reported (Ramma, 2011; Szarka et al., 2010). Szarka et al. reported elevated circulating IL-1 receptor antagonist concentration in women with a hypertensive disorder as an indication of increased levels of IL-1α and IL-1β late in pregnancy (2011). Additionally Szarka reported higher levels of IL-8 late in pregnancy, a finding contrary to our results.

Women with low stress scores without a hypertensive disorder had significantly higher levels of IL-1β, IL-10, and TNF-α. These finding contradict previous published results where IL-1β and IL-6 were higher in women experiencing higher levels of stress (Coussons-Read et al., 2007). It is important to mention the measure of stress in this study utilized a different instrument that may have not captured the same dimensions as the other study. In addition, the women in this study had relatively low stress scores while the women in the study by Coussons-Read et al. women equally distributed into low, average, and high stress groups.

Women experiencing a hypertensive disorder and high stress had higher levels of IL-6 in all trimesters similar to findings from Coussons-Read et al. (2005), higher levels of IL-8 in the second and third trimesters, and higher levels of IL-1α in the third trimester than the low stress group. When Il-8 was averaged over trimester for both groups, serum

levels were lower for those women categorized with high stress. To date no studies have measured IL-8 or IL-1α in the context of high stress in a hypertensive pregnancy. High levels of stress have been previously associated with a high-risk pregnancy such as one complicated with a hypertensive disorder (Cardwell, 2013). However, participants in this study did not report high levels of stress and a significant difference between the groups was not demonstrated.

Despite hypertension status, there was a significant interaction between stress level (high/low) and trimester for IL1-α only; women with high stress had lower levels of IL1-α in the first trimester compared to women with low stress. This finding does partially support the hypothesis proposed by Coussons-Read et al. that maternal perceived stress during the prenatal period has a negative effect on pregnancy outcomes by altering the maternal immune response (Coussons-Read et al., 2003). Stress level did have an effect on the pro-inflammatory marker IL1-α, but it was not a heightened response.

There was a significant interaction between stress level, hypertension status and trimester for IL-10 only. Serum levels of IL-10 were significantly higher in the third trimester in women with high stress and a hypertensive disorder compared to normotensive women with low stress levels. We do expect IL-10 production to be heightened in the third trimester until just prior to onset of labor in normal pregnancy (Moreli et al., 2012). However, this finding of an exaggerated anti-inflammatory response in the third trimester in hypertensive women with high stress is an indication of dysregulation of the inflammatory response and might be a compensatory mechanism (Szarka et al., 2010).

For this secondary data analysis, inflammatory biomarkers were measured from serum. Biomarker levels can also be measured in other mediums such as saliva and cervicovaginal fluid. Serum levels may not accurately capture differences between women developing a hypertensive disorder from those that do not while other mediums, such as cervicovaginal fluid, may be more representative of the physiological maternal response.

Limitations

As a secondary data analysis, the researcher has no control of the parent study rigor or sample population. A diagnosis of a hypertensive disorder was not an integral component of the parent study. Therefore, the sample size of women with a hypertensive disorder was small, especially when measuring longitudinally losing participants at each time point. Due to the sample size, most variables were categorized into smaller groups including the measure of stress. Preeclampsia was included in the hypertensive disorder group in order to increase the sample size; however, the resulting size was still too small and lacked statistical power. Although inflammatory biomarker data were evaluated for each trimester, there was variability in the serum measures. This could be due to the six-week collection window within each trimester; further, these concentrations may vary by gestational age.

Another limitation is the presence of recall bias with this type of study. The ESI is based on participant's recollection of stressful events and therefore an inaccurate assessment of their maternal stress might be measured. In addition, self-report and social desirability bias may also influence reported results. No other studies examining the

association between perceived maternal stress and hypertension during pregnancy used this instrument.

Conclusions

This study did not find significant differences between women with a hypertensive disorder and those without in either stress levels or biomarker levels. However, independently, categorized stress was associated with significant changes in biomarker levels at different trimesters of pregnancy for women with a hypertensive disorder and those without this disorder. Furthermore, hypertensive women with high stress experienced a heightened anti-inflammatory response compared to normotensive women with low stress levels, potentially a compensatory mechanism. The association of subjective stress and inflammatory biomarkers in the development of a hypertensive disorder is complex. Although the exact cause of these disorders is unclear, a maladaptation of the maternal immune response has been associated with the development of a hypertensive disorder and with a heightened stress response, specifically an exaggerated pro-inflammatory response. To understand this relationship more clearly further longitudinal studies with a larger sample size are warranted.

Tables

Table 3.1. Sample characteristics of women with a hypertensive disorder compared to normotensive women (n = 97)

Characteristic	Hypertensive disorder (n = 33), 34%	Normotensive (n = 64), 66%	P-value
Race			.935
Caucasian; n, %	25 (76%)	48 (75%)	
Not Caucasian; n, %	8 (24%)	16 (25%)	
Education			.526
High School or less; n, %	8 (24%)	12 (19%)	
Greater than high school; n, %	25 (76%)	52 (81%)	
Income			.901
≤ $29,999; n, %	14 (42%)	28 (44%)	
≥ $30,000; n, %	19 (58%)	36 (56%)	
Marital Status			.031*
Single/not living with partner; n, %	3 (9%)	18 (28%)	
Married/living with partner; n, %	30 (91%)	46 (72%)	
Age; mean ± SD	26 ± 4.3	25.9 ± 4.1	.988
ESI Composite Score (1st trimester); mean ± SD	4.9 ± 7.4	2.3 ± 4.2	.066

*significant to ≤ .05

Table 3.2. Mean levels of serum inflammatory biomarkers compared between hypertensive and normotensive groups in each trimester

Mean ±SD (pg/mL)	Trimester 1			Trimester 2			Trimester 3		
	Hypertension (n = 21)	**Normotensive (n = 42)**	**P-value**	**Hypertension (n=21)**	**Normotensive (n=42)**	**P-value**	**Hypertension (n=21)**	**Normotensive (n=42)**	**P-value**
IL-1α	**27.2±68.3 pg/ml**	**43.7±212.8 pg/ml**	**.630**	**16.5±38.6 pg/ml**	**22.2±82.9 pg/ml**	**.870**	**10.9±24.6 pg/ml**	**15.2±45.8 pg/ml**	**.688**
IL-1β	**3.7±9.2 pg/ml**	**5.0±18.6 pg/ml**	**.821**	**2.7±4.4 pg/ml**	**3.4±8.7 pg/ml**	**.713**	**2.3±3.1 pg/ml**	**5.4±12.0 pg/ml**	**.366**
IL-6	**60.2±162.2 pg/ml**	**12.6±46.1 pg/ml**	**.264**	**50.7±152.5 pg/ml**	**12.1±25.7 pg/ml**	**.261**	**32.7±97.5 pg/ml**	**16.3±34.5 pg/ml**	**.196**
IL-8	**15.1±24.1 pg/ml**	**12.8±15.8 pg/ml**	**.366**	**14.2±22.0 pg/ml**	**20.2±58.9 pg/ml**	**.578**	**13.4±15.2 pg/ml**	**17.2±20.9 pg/ml**	**.400**
IL-10	**48.6±143.4 pg/ml**	**21±38.2 pg/ml**	**.773**	**41.3±117.2 pg/ml**	**20.6±30.2 pg/ml**	**.462**	**18.6±32.6 pg/ml**	**16.8±31.1 pg/ml**	**.689**
TNF-α	**10.6±12.0 pg/ml**	**9.1±6.0 pg/ml**	**.901**	**11.7±8.9 pg/ml**	**13.4±15.5 pg/ml**	**.622**	**11.7±6.4 pg/ml**	**14.4±16.3 pg/ml**	**.994**

Table 3.3. Mean levels of serum inflammatory biomarkers compared between low and high stress scores in each trimester for normotensive women

Mean ±SD (pg/mL)	Trimester 1			Trimester 2			Trimester 3		
	Low Stress (n = 48)	**High Stress (n = 13)**	**P-value**	**Low Stress (n = 42)**	**High Stress (n = 12)**	**P-value**	**Low Stress (n = 35)**	**High Stress (n = 8)**	**P-value**
IL-1α	**7.9±19**	**122.6±379.1**	**.308**	**10.0±26.1**	**47.3±149.0**	**.859**	**23.5±55.5**	**6.4±10.4**	**.504**
IL-1β	**2.9±5.4**	**11.2±33.1**	**.403**	**4.2±8.9**	**3.5±9.9**	**.559**	**9.3±17.5**	**.8±.9**	**.006***
IL-6	**6.3±8.8**	**29.8±81.8**	**.624**	**11.2±19.0**	**20.7±41.1**	**.908**	**21.8±41.2**	**10.4±27.6**	**.106**
IL-8	**9.7±9.6**	**22.1±22.9**	**.074**	**18.7±59.0**	**15.4±12.9**	**.168**	**16.3±22.1**	**15.7±19.2**	**.728**
IL-10	**17.4±21.4**	**25.1±61.8**	**.123**	**22.9±33.9**	**22.7±38.8**	**.109**	**33.2±69.5**	**3.4±3.2**	**.005***
TNF-α	**12.0±11.7**	**6.7±4.5**	**.419**	**13.8±15.6**	**8.4±6.5**	**.326**	**16.5±17.4**	**8.5±7.2**	**.039***

*significant to ≤ .05

Table 3.4. Mean levels of serum inflammatory biomarkers compared between low and high stress scores in each trimester for hypertensive women

Mean ±SD (pg/mL)	Trimester 1			Trimester 2			Trimester 3		
	Low Stress (n = 20)	**High Stress (n = 10)**	**P-value**	**Low Stress (n = 19)**	**High Stress (n = 7)**	**P-value**	**Low Stress (n = 14)**	**High Stress (n = 11)**	**P-value**
IL-1α	**16.8±43.0**	**51.6±94.7**	**.271**	**8.0±18.5**	**29.5±60.7**	**.322**	**3.8±9.6**	**39.2±77.7**	**.048***
IL-1β	**3.4±6.7**	**6.1±13.0**	**.762**	**2.9±4.5**	**2.2±3.6**	**.981**	**2.0±3.5**	**3.1±4.4**	**.284**
IL-6	**14.7±30.9**	**122.7±223.9**	**.012***	**10.6±28.6**	**129.7±253.3**	**.001***	**5.6±8.1**	**63.2±132.2**	**.025***
IL-8	**17.0±31.5**	**26.6±31.6**	**.140**	**10.8±21.5**	**19.1±14.5**	**.034***	**9.7±14.6**	**18.5±17.1**	**.050***
IL-10	**21.0±34.4**	**79.5±206.3**	**.998**	**45.5±123.3**	**12.0±8.1**	**.850**	**13.6±17.1**	**100.6±268.8**	**.563**
TNF-α	**9.1±8.1**	**13.9±16.5**	**.380**	**10.0±5.3**	**13.2±14.2**	**.675**	**12.2±6.5**	**11.3±8.5**	**.496**

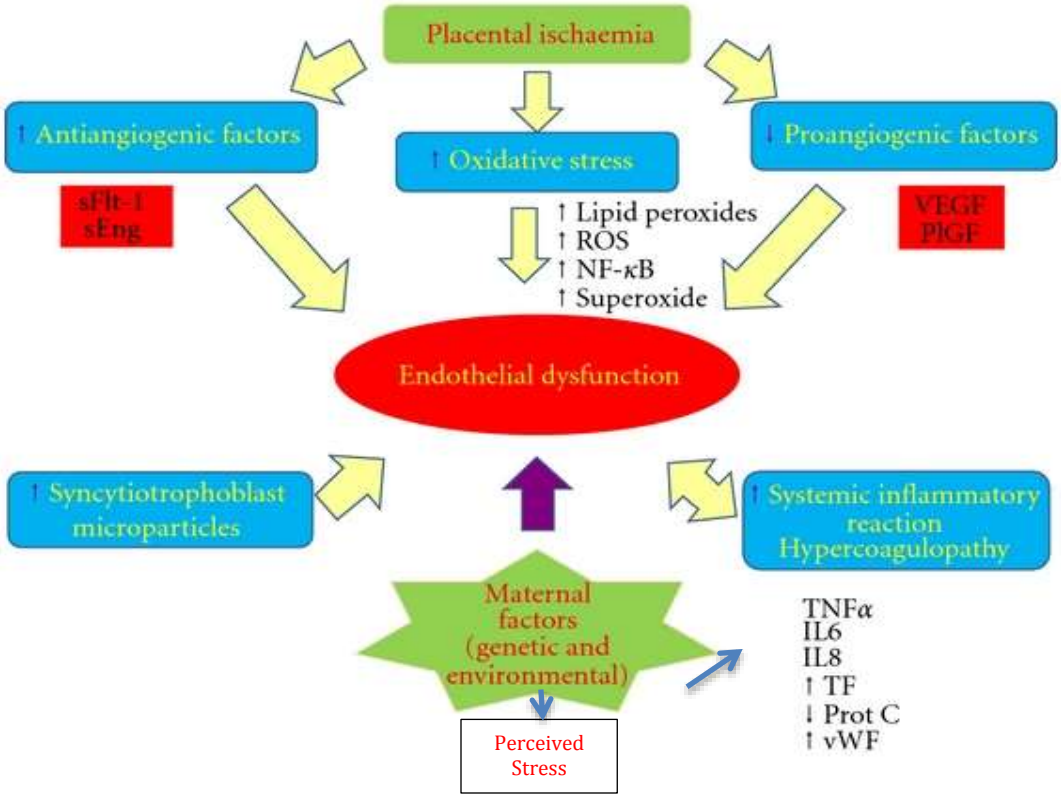
*significant to ≤ .05

Table 3.5. Repeated measure models for each inflammatory biomarker with main effects of hypertension (yes/no), stress (high/low) and trimester

	Serum	
	F	p
IL-1α		
Hypertension Status	0.01	0.93
Stress Level	2.17	0.14
Trimester	2.5	0.09
Stress x Trimester	**5.0**	**0.008***
IL-1β		
Hypertension Status	0.08	0.78
Stress Level	0.01	0.92
Trimester	1.13	0.32
IL-6		
Hypertension Status	3.39	0.07
Stress Level	2.72	0.10
Trimester	0.36	0.70
IL-8		
Hypertension Status	0.02	0.88
Stress Level	**7.57**	**.007***
Trimester	0.67	0.51
IL-10		
Hypertension Status	0.08	0.78
Stress Level	3.72	0.06
Trimester	0.15	0.86
Stress x Hypertension x Trimester	**3.33**	**0.04***
TNF-α		
Hypertension Status	0.25	0.62
Stress Level	0.80	0.37
Trimester	2.0	0.14

* significant to ≤ .05

Figure 3.1. Theoretical Framework Illustrating Factors Associated with the Development of Preeclampsia Symptoms



Chapter IV: A Review of the Association of Psychological Distress with the Development of a Hypertensive Disorder during Pregnancy

Background and Significance

Hypertensive disorders complicate up to 10% of pregnancies and are associated with higher rates of maternal and fetal morbidity and mortality (American College of Obstetricians and Gynecologists, 2013). Hypertensive disorders consist of several classifications including chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia. A World Health Organization review identified these disorders as the leading cause of maternal mortality accounting for 16% of deaths in industrialized countries (Khan, Wojdyla, Say, Gülmezoglu, & Van Look, 2006), and are associated with an increased risk of stillbirth (Hutcheon, Lisonkova, & Joseph, 2011). In addition, women with preeclampsia are at an increased risk (10-30% higher) for severe complications including acute renal failure and pulmonary edema (Wallis, Saftlas, Hsia, & Atrash, 2008). Infants of mothers with preeclampsia are at two times increased risk of low Apgar scores and three to four times increased risk of being small for gestational age, an effect that is more pronounced at preterm gestation than term (Hutcheon et al., 2011). Given the severity of these disorders, understanding the etiology of hypertensive disorders remains an important objective.

Overall, the exact etiology of hypertensive disorders, including preeclampsia, is unknown. However, there are physiological (immunity and placental ischemia) and psychological (stress, anxiety, depression) factors that have been associated with the development of these complex disorders (Lazdam et al., 2011). Furthermore, psychological stress has been directly associated with the development of a hypertensive disorder (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009) as well as through

altering maternal immune function. Vianna et al., (2011) hypothesized that distress conditions including stress, anxiety, and depression can induce a hypertensive disorder in part through maternal dysregulated immunity (Vianna et al., 2011). Prior research has focused on one component of psychological distress, primarily stress and the associations among women experiencing a subsequent development of a hypertensive disorder during pregnancy (Klonoff-Cohen, Cross, & Pieper, 1996; Landsbergis & Hatch, 1996; Yu et al., 2013). Psychological distress includes stress but also anxiety and depression. Studies have reported on all three components to varying degrees.

Prevalence of psychological distress in pregnancy have been reported between 13 and 25% (Çapik & Pasinlioglu, 2015). Breaking psychological distress into components, antenatal depression has a reported prevalence of 14 – 23% (Yonkers et al., 2009); estimates of antenatal anxiety are not known; however, women have reported anxiety during pregnancy (Schetter & Tanner, 2012), and the March of Dimes reported nearly 75% of women experienced at least one stressful event in the 12 months prior to delivery (March of Dimes, 2015).

There has been a breadth of studies describing both independent and multiple (two or more) psychological distress factors associated with hypertensive disorders during pregnancy. Of the studies examining an independent psychological distress factor, maternal stress has been the most researched. In a recently submitted review Kehler (2016) identified stress as a risk factor in the development of a hypertensive disorder (Kehler, 2016). Greater perceived lifetime stress and stress during pregnancy were associated with an increased risk of preeclampsia (OR, 2.1; CI, 1.6 – 2.9 and OR, 1.7; CI, 1.3 – 2.2) (Yu et al., 2013), Furthermore, stress was associated with the progression of a

hypertensive disorder during pregnancy. Stress levels were significantly higher in women with worsening symptoms of preeclampsia compared to those women with a milder condition (Black, 2007). Similar to these findings, a published meta-analysis of 12 studies examining the association of maternal stress and preeclampsia reported, mental stress was associated with an increased risk of preeclampsia (OR, 1.49; CI, 1.27 – 1.74, $p < 0.001$) and pooling 4 studies using gestational hypertension as the outcome showed similar results (OR, 1.26; CI, 1.00 – 1.59, $p = 0.047$) (Zhang et al., 2013). Mental stress was defined as work stress, job strain, pregnancy-related stress, life stress, perceived stress, and psychosocial stress (Zhang et al., 2013). Due to the majority of published research focusing on stress and the author's recent review of stress, the author will report findings from this study breadth and stress will not be a primary component of this review.

There were fewer studies (n= 6) describing the association between depression and/or depressive symptoms and prenatal hypertensive disorders, and of those, results were conflicting. While three studies did support a relationship between depression and the development of a hypertensive disorder (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009) three others did not (Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2004; Thombre, Talge, & Holzman, 2015; Vollebregt et al., 2008).

Maternal anxiety during pregnancy has received the least attention of the psychological distress factors contributing to the development of a hypertensive disorder when compared to maternal stress and depression. Prior studies suggest that anxiety symptoms may develop or be exacerbated during pregnancy (Breitkopf et al., 2006). However, results vary with three studies' results supporting a relationship between

anxiety and the development of a hypertensive disorder (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009) and four that did not find a significant association (Andersson et al., 2004; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008).

Although researchers have reported on psychological distress, few have utilized a conceptual framework in their studies. A conceptual framework would organize ideas and identify key relationships between variables. Since stress, a component of psychological distress has been shown to increase the risk of developing a hypertensive disorder during pregnancy and anxiety and depression can be related to stress and are components of psychological distress; it seems pertinent to investigate any relationship between depression and/or anxiety in a hypertensive disorder. The purpose of this paper was to operationally define the components of psychological distress, identify the prevalence of psychological distress, and examine any associations of psychological distress with the development of a hypertensive disorder during pregnancy. The specific aims were as follows:

1) Investigate three primary components of psychological distress within a conceptual framework during pregnancy

2) Determine the prevalence of the least investigated components of psychological distress (anxiety, and depression) with the development of a hypertensive disorder

3) Examine and evaluate the literature combining at least two components of psychological distress (stress, anxiety and depression) with the development of a hypertensive disorder during pregnancy.

In this paper, hypertensive disorders in pregnancy include gestational hypertension and preeclampsia.

Concepts of Psychological Distress and Conceptual Framework

Prior to reviewing the literature, it was important to operationally define the concepts of maternal stress, anxiety, and depression in the context of pregnancy including pregnancy complications and identify a conceptual framework to direct the study.

Stress: Selye (1956) defined stress as the representation of the effects of anything that threatens homeostasis. The actual or perceived threat is a stressor, and the response to the stressor is the stress response (Selye, 1956). Since then, many terms and labels for stress have been used, measured, and reported in the literature; however, conceptual and operational definitions are often not provided. For example, Sikkema et al., measured 'psychological stress' using salivary cortisol and measured anxiety but did not provide a definition for psychological stress (Sikkema et al., 2001). Terms used to describe stress included 'general life stress', 'perceived stress', 'violent events', 'work stress', 'job stress', 'chronic stress', 'psychosocial stress', 'general distress', and 'pregnancy-specific stress' (Christian, 2012a; Klonoff-Cohen et al., 1996; Landsbergis & Hatch, 1996; Schetter & Tanner, 2012; Yu et al., 2013). Still other's report stressors, or strain to describe the emotional experience that initiates a response (Schetter & Tanner, 2012). Differing conceptual definitions of maternal stress during pregnancy pose limitations when comparing studies. In addition, various self-report instruments are utilized to assess the associated symptoms for a multitude of stress concepts leading to difficulties in interpreting and comparing severity of the symptoms among articles. The National Institution of Mental Health (NIMH) defines stress as the brain's response to any demand

(U. S. Department of Health and Human Services). Stress can be caused by routine stressors such as work, family, and other daily responsibilities or hassles. Stress can also be caused by non-routine stressors such as a sudden change like losing a job or having an illness or by a major event like a natural disaster or assault (U. S. Department of Health and Human Services). For the purposes of this review the operationalized definition of stress is a psychological feeling of pressure from a stressor. This definition is inclusive and incorporates pressure from all three categories defined by NIMH.

Anxiety: The NIMH defines anxiety as temporary worry or fear. It can be characterized as either state (how an individual feels right now) or trait (evaluates an individuals' propensity for anxiety) (Julian, 2011). General anxiety can be measured with several validated self-report instruments commonly used to assess symptom severity. An anxiety disorder occurs when the fear or worry does not go away and can get worse over time and these feelings may start to interfere with everyday life and relationships (U. S. Department of Health and Human Services, 2016a). In addition, exposure to stressful life events is a risk factor for the development of an anxiety disorder. Assessing an anxiety disorder requires other measures used to evaluate specific diagnostic criteria for each disorder. Anxiety has fewer; more clearly defined terms and associated symptoms. For the purpose of this review all levels of anxiety were included.

Depression: The NIMH defines depression as experiencing some of the following symptoms: persistent sad or anxious moods, feelings of hopelessness, worthlessness, fatigue, loss of interest in hobbies, and activities, difficulty sleeping, among others (U. S. Department of Health and Human Services, 2016b). Depression is a common mood disorder on a continuum based on time and severity of symptoms. Perinatal depression

can also be mild to severe and be experienced during pregnancy or after the birth of their baby. Several self-report instruments have been validated for use in measuring the severity of depressive symptoms and a few are frequently used in the literature regarding depression during pregnancy. Maternal depression during the perinatal period rather than the postpartum period was examined in this review.

A concept analysis by Emmanuel and St. John (2010) provided some clarity in the terms often used to describe maternal distress. Again, several terms were used in lieu of the term "maternal distress", however few provided conceptual definitions. Terms used including: 'distress', 'mental distress', 'distressed mood', psychological distress', 'emotional distress', 'prenatal maternal stress', and 'depressive and anxiety symptoms' (Emmanuel & St John, 2010). Although several terms were used to describe the phenomenon, the emerging themes included stress or distress, depression and anxiety (Emmanuel & St John, 2010). The authors go on to define maternal distress as a continuum including the stress response as either stress (worry, concern, mild anxiety) as mild distress to anxiety and depression (unhappy, low mood, highly anxious) as high distress (Emmanuel & St John, 2010). The continuum model is ideal as symptoms of stress, anxiety, and depression can overlap without clear separations. For the purposes of this review, psychological distress will describe any point on this continuum and is comprised of stress, anxiety, and depression.

Conceptual Framework: The concept of psychological distress fits in with the Psychoneuroimmunology (PNI) model in pregnancy put forth by Christian (2011). The PNI model incorporates psychological distress with maternal health, birth outcomes, and fetal development through maternal immune parameters. The PNI model includes

stressors, coping resources as moderators, the resulting psychological distress and the health behaviors associated, the resulting immune response, and lastly maternal health and pregnancy outcomes (Christian, 2012b). The components of psychological distress include stress, anxiety, and depression. The maternal outcome is not specified but for this review, the outcome is a hypertensive disorder. The original model did not address any direct links between psychological distress and maternal health, but evidence has supported a relationship between these two factors; therefore, it is that relationship the author is investigating in this review (Yu et al., 2013). Figure 4.1 contains the PNI framework with the relationships studied for this review.

Literature Search Strategy

The author conducted a search for published, peer-reviewed, English language, primary research articles using the electronic databases Medline, CINAHL, Psychology and Behavioral Sciences Collection, and PsychINFO and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). Initial key search and MeSH terms included *preeclampsia* or *pregnancy-induced hypertension* or *PIH; self-reported stress* or *maternal stress* or *perceived stress* or *stress, psychological; anxiety;* and *depress**. Subsequent searchers were conducted with *preeclampsia* or *pregnancy-induced hypertension* or *PIH* and each of the other terms independently. Inclusion criteria were as follows: quantitative or qualitative research studies on the relationship between at least two of the following self-reported, perceived, and/or psychosocial stress, anxiety, and/or depression in adult women with a hypertensive disorder during pregnancy and study occurred during pregnancy. The search was limited to current literature, published between January 2008

and 2016 (present) to reveal the most recent knowledge. The start date of 2008 was based upon the first located article to include at least two of the psychological stress variables. The aforementioned criteria yielded 152 articles. After deleting duplicates, 129 remained. The remaining titles and abstracts were screened for suitability leaving 27 for full text review. A hand search of references resulted in the addition of three more articles. Studies were excluded if performed after delivery, measured newborn/child outcomes, if study included substance abuse, rape, intimate partner violence or was associated with a natural disaster, or identified stress, depression, and/or anxiety prior to conception. Following full text review, seven articles remained that met inclusion criteria for this review. See Figure 4.2 for a diagram of the decision-making process.

A matrix table of the selected articles organized the literature (Table 4.1). The matrix table headings included: author, year, and title, setting and design, sample and time of assessment, measures, results, strengths and limitations, and variables controlled. Findings from the literature were synthesized, summarized, and critically appraised to expose current gaps in the literature and recommendations for future research.

Results

Characteristics of Studies Reviewed

There was a significant lack of studies that included at least two aspects of psychological distress; therefore, the search was expanded to include 15 years (2000 and 2015). Seven studies met inclusion, and represented five countries including the United States, Netherlands Finland, Sweden, and Brazil. The common aim shared among the studies was to examine the relationship of psychological distress and the development of a hypertensive disorder during pregnancy. The primary study characteristics for this

review included study design, sample features and time point of measurement, measures used, results, and limitations. Table 4.1 provides a description of the study characteristics included in this review.

While the type of study was the same for the seven studies, methods differed. Of the reviewed studies, researchers used a quantitative design. The majority of the studies were limited through utilizing a cross-sectional prospective study design (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Thombre et al., 2015; Vollebregt et al., 2008); whereas Sikkema et al's study was strengthened by using a case controlled longitudinal design (Sikkema et al., 2001). In these studies, researchers set significance a priori at $p = 0.05$. A fundamental weakness was a lack of conceptual framework to guide any of the research presented in this review. Recruitment methods varied; some women were recruited from hospitals during ultrasound visits, prenatal clinics, along with obstetrics and gynecology clinics.

Sample sizes and features differed among the studies. A total of 9,892 women participated in the seven studies and the sample size ranged from 18 to 3679. The studies included a mix of social demographics. Study participants were all white or a majority were white women (Kurki et al., 2000; Qiu et al., 2009; Sikkema et al., 2001) while others were more ethnically diverse (Franco et al., 2015; Thombre et al., 2015; Vollebregt et al., 2008), or race was not reported (Andersson et al., 2004). Most women were married, did not smoke, worked and had an income larger than the minimal wage per capita (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Vollebregt et al., 2008) with the exception of one study where more than half of the women were on Medicaid (Thombre et al., 2015). The women in three of the studies were

nulliparous (Kurki et al., 2000; Qiu et al., 2009; Sikkema et al., 2001; Vollebregt et al., 2008) while three included women who have given birth before (Andersson et al., 2004; Franco et al., 2015; Thombre et al., 2015). Data collection time points varied as well. Women were approached for recruitment and measures were taken beginning at 10 weeks gestation through the third trimester.

Psychological Distress Measures

The components of psychological distress were assessed almost exclusively by subjective, self-report measures (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). A few relied on medical record evaluations (Franco et al., 2015; Qiu et al., 2009), and one included a structured interview by the provider after participants completed a questionnaire (Andersson et al., 2004). Measures of a hypertensive disorder during pregnancy were gathered through medical records for most of the studies except for one that assessed "momentary hypertension" through the use of a digital blood pressure monitor (Franco et al., 2015). Sikkema et al. strengthened their study by including a biological measure for psychological distress in addition to the self-report measures (Sikkema et al., 2001).

*Stress Measures***:** Only one form of stress was evaluated in these studies. Work stress was examined using four scales; reliability and validity were not mentioned for any one instrument but Cronbach's α was given for the total scale (Vollebregt et al., 2008).

*Depression Measures***:** Depression was measured or assessed with a few self-report instruments, medical records, or questions asked to study participants. Studies were strengthened through using well-known instruments such as Beck Depression Inventory (BDI) (Kurki et al., 2000) and the Center for Epidemiologic Study Depression

(CESD) scale (Thombre et al., 2015; Vollebregt et al., 2008) and provided evidence of reliability using Cronbach's α as well as validity (Kurki et al., 2000; Vollebregt et al., 2008). In one study, however, depression was included as a variable but the authors did not mention how they assessed participants for depression (Franco et al., 2015). Depression was also evaluated using the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire and reported as "has been validated for use in obstetric-gynecologic patients" (Andersson et al., 2004).

Anxiety Measures: Anxiety was primarily measured with the State - Trait Anxiety Inventory (STAI) questionnaire, English and Dutch versions (Franco et al., 2015; Sikkema et al., 2001; Vollebregt et al., 2008). When reliability was reported, it was through using Cronbach's α; yet others did not report reliability. Few used the state measure (Franco et al., 2015; Vollebregt et al., 2008) while one used both state and trait scores (Sikkema et al., 2001). Two studies measured pregnancy specific anxiety using an abbreviated version of the pregnancy-related anxiety questionnaire (PRAQ) and the author's provided validity data in the form of factor analyses and reliability using Cronbach's α (Sikkema et al., 2001; Vollebregt et al., 2008). Studies were weakened when they did not use valid instruments to assess anxiety or relied on medical records (Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015). Anderson et al. measured a more severe form of anxiety. Anxiety disorders were assessed using the Primary Care Evaluating of Mental Disorders Patient Health Questionnaire; however, evidence of validation was not reported rather stated by the authors as "has been validated for use in obstetric-gynecologic patients" (Andersson et al., 2004). Sikkema et al. strengthened their study by including a biological measure of psychological stress (Sikkema et al., 2001).

Salivary cortisol was assessed for correlation to anxiety levels since it is a hormone that is excreted in excess during times of psychological stress. The authors provided sensitivity of equipment measuring cortisol levels.

Hypertensive Disorders in Pregnancy Measures: Preeclampsia and gestational hypertension were the two disorders included in this review. Preeclampsia was most often diagnosed after having diastolic blood pressure (DBP) ≥ 90 mmHg or systolic blood pressure (SBP) ≥ 140 mmHg on at least two different calendar days plus evidence of proteinuria (≥ 300 mg per 24 hrs.) after 20 weeks gestation. Gestational hypertension has the same diagnostic criteria without proteinuria. Slight variations in diagnostic criteria were only using DBP (Vollebregt et al., 2008), DBP of 100 mmHg (Kurki et al., 2000), only having one measure of blood pressure (Franco et al., 2015), or relying on medical record without specifying criteria (Qiu et al., 2009).

Study Findings

In total, seven studies have investigated the role of higher levels of at least two components of psychological distress (stress, anxiety, and/or depression) in the development of a hypertensive disorder during pregnancy with conflicting results. While significant positive associations between a measure of psychosocial distress and the development of a hypertensive disorder during pregnancy were found (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009); conversely, there was research that did not support this finding (Andersson et al., 2004; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008).

Studies reporting a positive association between psychological distress and a hypertensive disorder provided different statistical evidence. Women experiencing

higher levels of anxiety were more likely to have hypertension compared to women without anxiety (p = 0.049) (Franco et al., 2015). Women were also at an increased risk for developing a hypertensive disorder in the presence of a psychological distress (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009). Associations between psychological distress and a hypertensive disorder were found at various times during pregnancy. In these latter studies, depression and anxiety were assessed at varied times during pregnancy: including two between the first and second trimester (Kurki et al., 2000; Qiu et al., 2009), and another in the third trimester (Franco et al., 2015). In a Finnish cohort, elevated depression scores as well as anxiety scores assessed at a median of 12 weeks gestation (first trimester) were associated with an increased risk for preeclampsia (adjusted OR 2.5, CI: 1.4 – 5.4) and (OR 3.2, CI: 1.4 – 7.4) respectively (Kurki et al., 2000). Similarly, Qiu et al., (2009) reported an increased risk of developing a hypertensive disorder when prenatal depression or anxiety was diagnosed prior to 20 weeks gestations (second trimester) (adjusted RR 2.12, CI: 1.02 – 4.45; p = 0.045). Additionally, women diagnosed with a depressive disorder alone were also at an increased risk (RR 2.72, CI: 1.29 – 5.74; p = 0.009).

Study results did not always support a positive association between psychological distress and the development of a hypertensive disorder. The majority of the studies (n=4) that combined two psychological distress measures did not find an association. Anxiety or depression assessed between 16 and 27 weeks gestation had no effect on the development of a hypertensive disorder during pregnancy (Andersson et al., 2004; Thombre et al., 2015; Vollebregt et al., 2008). Vollebregt et al. (2008) reported maternal stress (operationalized as work stress) did not increase the risk of developing a

hypertensive disorder after adjustment of covariates (Vollebregt et al., 2008). Finally, neither of the two measures of anxiety (STAI or PRAQ-R) nor salivary cortisol levels were different in women who developed a hypertensive disorder when compared to controls, regardless of gestational ages (Sikkema et al., 2001).

Prevalence of the components of psychological distress varied in these studies as well. Four of the studies reported depression prevalence and four reported anxiety prevalence. The prevalence of depression ranged from 4.2 to 35% (Andersson et al., 2004; Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015), anxiety 1.2 to 16% (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009). It is important to note the lowest prevalence for both anxiety and depression was with the diagnosis of a disorder. Additionally, one study reported 92% of those in their study had an anxious personality, but they did not specify what cut-off was used to determine an anxious personality (Franco et al., 2015). Also, the high prevalence did not translate into their tables so determining the actual prevalence was not possible.

Strength and Limitations of Evidence

The studies reviewed had several strengths as well as limitations. The strengths included timing of data collection, using control groups, controlling for confounding variables, and using valid instruments for measuring psychological distress. Assessing psychological distress prior to the symptoms of a hypertensive disorder i.e. before 20 weeks gestation (Andersson et al., 2004; Kurki et al., 2000; Qiu et al., 2009; Sikkema et al., 2001; Thombre et al., 2015) allows the researcher to examine the risk factors for the development of the disease. Another strength was the use of control groups; however, the sample sizes varied considerably. A strength of most of the studies was controlling for

variables that were associated with the development of a hypertensive disorder. Variables controlled included pre-pregnancy BMI, age, and ethnicity (Qiu et al., 2009; Thombre et al., 2015; Vollebregt et al., 2008). Two did not include race since their sample was all white (Andersson et al., 2004; Kurki et al., 2000). Others controlled for smoking as well (Andersson et al., 2004; Kurki et al., 2000; Thombre et al., 2015; Vollebregt et al., 2008). Lastly, strengths of some of the studies reviewed were the measures used to collect the data. Valid instruments for measuring psychological distress were used by several researchers (Kurki et al., 2000; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). Furthermore, Vollebregt et al. (2008), strengthened their study by completing a comprehensive evaluation of psychological stress during pregnancy by measuring depression, anxiety, and work stress; yet another strengthened their study through the use of a biological measure (Sikkema et al., 2001) The biological measure did demonstrate reliability. The method for collecting salivary cortisol was reliable by following a demonstrated salivary protocol for collecting and storing saliva and testing cortisol levels (Sikkema et al., 2001).

Another strength of all but one of the studies was the diagnosis of a hypertensive disorder was verified through medical records and not reliant on self-report. However, one study did not meet the criteria for gestational hypertension having relied on one measure of blood pressure at one time point (Franco et al., 2015).

There were also limitations in the studies reviewed. Limitations included data collection timing, sample sizes, and measures used to collect data. Timing of data collection was a limitation when there was a potential overlap of the development of the hypertensive disorder and collection of the psychological distress data (Franco et al.,

2015; Vollebregt et al., 2008).While prospective design allows for a predictive model for the development of a hypertensive disorder during pregnancy; when data collection occurred after 20 weeks gestation, there was a chance the women may have had preeclampsia prior to the collection of psychological distress and having the condition could alter their responses to the assessment. There was another limitation to collecting at one time point. Assessing psychological distress at one time point fails to capture any changes in the levels of this distress. For example, it was impossible to determine if increasing severity of stress, depression, and/or anxiety correlate with the severity of the hypertensive disorder in pregnancy in most of these studies (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015; Vollebregt et al., 2008).

Another limitation was sample size. Most of the studies had small sample sizes ranging from 9 – 66 women who developed a hypertensive disorder (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Sikkema et al., 2001). One study had a large sample size of 289 with a hypertensive disorder, but after separating in to low, moderate, and high levels of psychological stress the confidence intervals of the risk estimates were large and odds ratios failed to reach statistical significance (Vollebregt et al., 2008).

Lastly, the measures used to collect the data were a limitation. Researchers relied on self-reported data without clinical or biological verification (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). Some did not provide cut-off scores of instruments used (Franco et al., 2015; Vollebregt et al., 2008), most did although one score used was very low.

Kurki et al. utilized a modified BDI and a very low cut-off score of three as an indication of depression. Thus their prevalence of depression during pregnancy was 30%; an amount higher than the 14% reported by the American College of Obstetricians and Gynecologists (ACOG) thereby possibly altering the positive predictive value. Furthermore, Franco et al. did not rely on the ACOG definition of hypertensive disorders in pregnancy, but assessed blood pressure at one time point and used this measure in their analysis (Franco et al., 2015).

Risk of Bias

Several study biases exist in the reviewed studies, including sampling and observational bias, and use of self-reported measures. A common bias with these studies results from using convenience samples and not a population sample. This is a common finding in research with pregnant women due to pregnancy's transient nature but leads to the inherent problems of sampling bias and generalizability of results to a population. Inconsistent timing of measurement across studies and the use of cross-sectional data used in most of the studies increase the risk of observational bias. Without the ability to detect change over time, there was no way to assess the stability or instability of a particular psychological distress component. Self-reporting can lead to underestimating or overestimating a condition without any clinical or biological verification, and was only reported as a limitation in one study (Vollebregt et al., 2008). The limited use of biomarkers associated with psychological distress reviewed in these studies is noteworthy, as Sikkema et al. (2001) was the only study to use a biological measure to correspond with reported anxiety.

Discussion

According to the PNI framework during pregnancy, three primary components of psychological distress are stress, anxiety, and depression. Additionally, those components have been shown to have an effect on the development of a hypertensive disorder in some studies, while others did not support this claim. The association of psychological distress with the development of a hypertensive disorder remains unclear, likely due to differences in study design and operational differences of psychological distress.

Differences in study design including time point of assessment, sample size and controlled variables may account for conflicting results. Of the reviewed studies, a cross-sectional design was the most frequent; however, the time point of assessment altered with the studies. Most of the studies assessed psychological distress in the first or early in the second trimester (Andersson et al., 2004; Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015), while others assessed late second trimester or into third trimester (Franco et al., 2015; Vollebregt et al., 2008), and still another assessed before and after the potential development of symptoms (Sikkema et al., 2001). Furthermore, some studies held a tight window for assessment 1 to 2 weeks (Andersson, Sikkema, Thombre), one a more open window, 10-17 weeks (Kurki et al.) and others were anytime after a specific gestational age (Vollebregt, Qiu, Franco). The wide distribution of assessment points makes comparison of results difficult. Additionally, there was a lack of studies with assessments at more than one time point. Psychological distress changes throughout pregnancy. Depression levels fluctuated in each trimester, peaking in the second trimester (Bennett, Einarson, Taddio, Koren, & Einarson, 2004). Measuring psychological distress at one time point would not capture these changes. Sample sizes and prevalence rates

differed among these studies. Prevalence rates of depression ranged from 4.2 to 35%, and anxiety 1.2 to 16% (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015). Small prevalence rates for psychological distress and the development of a hypertensive disorder may have led to difficulty in demonstrating significance especially at the highest levels of stress, anxiety, and depression (Sikkema et al., 2001; Thombre et al., 2015). Moreover, while most controlled for confounding variables, psychotropic medications were not controlled for during data analysis (Qiu et al., 2009) and these type of medications have been independently associated with an increased risk of preeclampsia (Palmsten, Setoguchi, Margulis, Patrick, & Hernández-Díaz, 2012).

Differences were also noted with the operationalized definitions of psychological distress leading to differences in study results. Instruments were used in this review such as BDI, CESD, STAI, PRAQ-R, thereby operationalizing stress, anxiety, and depression differently. For example Sikkema et al. (2001), operationalized anxiety as associated with pregnancy and measured with the PRAQ-R differing from state anxiety where anxiety can occur from other stressors not related to pregnancy. In addition, levels of psychological distress were not the same in each study. An example was in Kurki et al's use of a low cut-off point increasing the prevalence of the psychological distress; still others did not provide evidence of validity in their selected instruments or relied on medical records (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Thombre et al., 2015).

Limitations

Limitations in this review may have also contributed to lack of consensus. The search methodology may have limited the number of studies identified for inclusion. The author was interested in psychological distress and therefore included only those studies that measured at least two components of psychological distress. In doing so, the only form of stress identified was in the form of routine stressors and was work related stress. Specifically, the search terms used may not have been inclusive enough to capture all the articles published on this topic. Another limitation was restricting hypertensive disorders to just preeclampsia and gestational hypertension omitting other disorders.

Recommendations for Future Research

Future research should consider study design, using a conceptual framework, use of valid instruments and pay careful attention to the components of psychological distress. In considering study design, longitudinal cohort studies with prospective maternal assessment are preferred. However due to the prevalence of a hypertensive disorder during pregnancy with concurrent symptoms of psychological distress, a case-control method may offer the best approach. Using an appropriate conceptual framework is also important to guide future studies. The purpose of a conceptual framework is to identify the variables central to the study and a framework for interpreting results. The psychoneuroimmunology framework in pregnancy could serve this purpose. Finally, the use of valid instruments and a biological or clinical measure in assessment of psychological distress is suggested. Discrimination between levels of anxiety and depression and general levels of stress cannot be easily assessed. These concepts overlap and include mood and anxiety disorders. They are often comorbid conditions as well.

Therefore, it is important to carefully assess each component of psychological distress with the appropriate validated measure. Using reliable and measurable instruments of psychological distress along with a biological measure (if feasible) is important in order to strengthen the reliability of the data. Self-report measures may suffice in assessing psychological distress but clinical interviews may better capture their psychological state. For example, mothers reported less psychological distress symptomology on self-report measures than during clinical interviews (Parcells, 2010).

Disentangling the effects and severity of the components of psychological distress on maternal outcomes such as hypertension during pregnancy is warranted. However, future studies should be robust in design.

Table 4.1. Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
Anderson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2013)	Sweden/ prospective descriptive	N = 1495; 16-18 weeks gestation	Primary Care Evaluation of Mental Disorders, self-report	Depressive disorders were most common, prevalence 11.6%; anxiety prevalence 6.2%; no correlations between depression and/or anxiety and a hypertensive disorder	2. Sample size too small to detect rare adverse events 2. Assessed at one time point 2. Excluded women were of lower socioeconomic status	Age, parity, marital status, socioeconomic status, smoking, pre-pregnancy BMI, chronic disease, history of miscarriage
Franco, R. C., Ferreira, C. R., Vieira, C. R., & Silva, R. R. (2015)	Brazil/Cross sectional	N = 105; 28 weeks to birth	State-Anxiety Inventory and a clinical-behavioral questionnaire, self-report	There was a difference between those with anxiety and the development of hypertension (p = 0.049); Same for depression (p = 0.011) Depression increased likelihood of hypertension	1. Higher levels of anxiety have been seen in 3rd trimester 2. Information in text does not match with information in tables 2. Analysis does not match up with tables presented 2.Small sample size	Not specified

Table 4.1 (Continued). Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
				(OR 8.69; CI 1.19 – 63.42, p = 0.033) Anxiety increased likelihood of hypertension (OR 7.77; CI 1.19 – 50.45, p = 0.032)	2. Assessed at one time point 2. Did not provide reliability/validity of instruments or cut points used 2. A hypertensive disorder could not be determined because blood pressure was assessed only once	
Kurki, T., Hiilesmaa, V., Raitasalo, R., Mattila, H., & Ylikorkala, O. (2000)	Finland/prospective	N = 623; 10-17 weeks gestation and at birth	Modified Beck Depression Inventory and one question about anxiety ("Are you tense or distressed?"), self-report	Depression (>4.5 in BDI) in 30%; anxiety in 16%; OR for preeclampsia in women with depression = 2.5, with anxiety = 3.2, combined = 3.1	1. Depression and anxiety were assessed prior to signs of preeclampsia 2. Assessed at one time point 2. Small sample size 1 or 2. Cohort included one demographic	Age, marital status, bacterial vaginosis, smoking, alcohol use, and profession

Table 4.1 (Continued). Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
Qui, C., Williams, M. A., Calderon-Margalit, R., Cript, S. M., & Sorensen, T. (2009)	US/retrospective	N = 2601; pregestational and prior to 20 weeks gestation	Medical records and self-reported medical histories	Prevalence of depression, bipolar or anxiety 5.2% of that 22% were diagnosed during first 20 weeks gestation; Depression, bipolar or anxiety had RR for preeclampsia was 2.86 p = 0.003, adjusted RR was 2.12 p = 0.045; Depression or bipolar had RR 2.72 p = 0.009; disorders diagnosed during the first 20 weeks were more strongly related with preeclampsia risk with adjusted RR was 3.64 p = 0.030	1. Assessed prior to signs of preeclampsia 2. Two few isolated anxiety or comorbid cases to estimate preeclampsia risk 2. 87.5% of those with psychological disorders were on medications, authors did not assess risks for those not on medication 2. Use of medical records to obtain mental health status but no mention of specific instrument used in screening	Age, race, income, parity, marital status, diabetes, hypertension, employed, alcohol use, exercise, pre-pregnancy BMI (altered unadjusted relative risks by ≥ 10%); adjusted RR included age, race, and pre-pregnancy BMI

Table 4.1 (Continued). Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
					2. Low prevalence of psychological disorders, possible cases undetected 2. Small sample size (only 9 subjects with preeclampsia and any psychological disorder)	
Sikkema et al. (2001)	Netherlands/ prospective case control matched for BMI, age, smoking, medication, race, parity, history of miscarriage, preeclampsia, diabetes or hypertension	N = 18 women (9 who developed preeclampsia and 9 matched controls); 17-18 and 27-28 weeks gestation	State-Trait Anxiety Inventory (Dutch version) and Pregnancy-related Anxiety Questionnaire, self report; salivary cortisol	Prevalence of anxiety was 3.6%; Stress as evident by salivary cortisol levels was not different between cases and controls; there were no differences in state, trait, or pregnancy-specific anxiety scores and the development of preeclampsia	1 or 2. All white women 2. Small sample size 2. Anxiety scores were low except for 1 2. Perceived stress was not assessed and may have an effect	

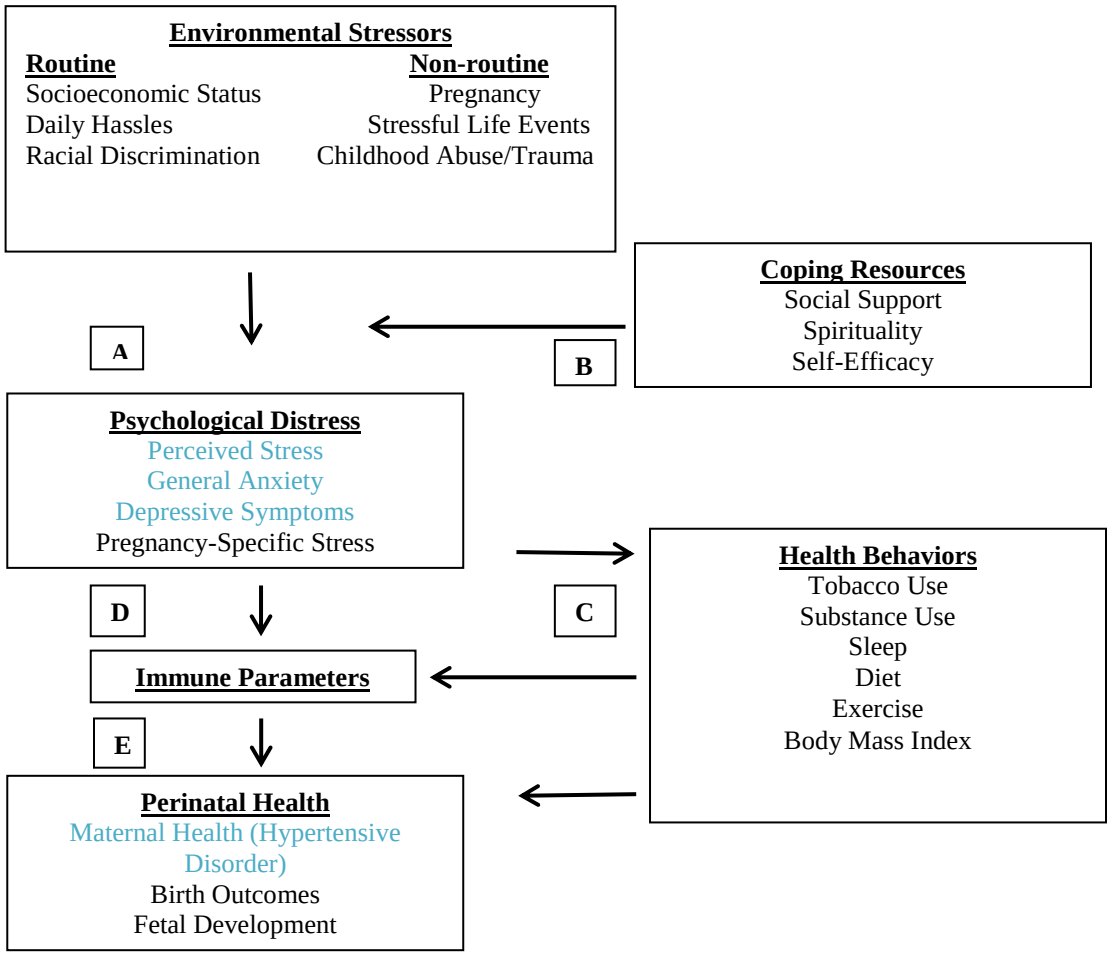
Table 4.1 (Continued). Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
				between cases and controls		
Thombre, M., Talge, N., & Holzman, C. (2015)	US/ retrospective	N = 1371; lifetime history, one year prior to pregnancy, since last menstrual period, and within the past week; 16-17 weeks gestation	Center for Epidemiologic Study Depression scale, self-report and medical report of antidepressant/ antianxiety medication prescription during pregnancy	Prevalence of depressive symptoms during past week was 35%; depressive or anxiety symptoms since last menstrual period was 5%; depressive or anxiety symptoms in past week or since last menstrual period were not significant risk factors in the development of hypertensive disorders	1. Demographic characteristics were well distributed 2. Last assessment was in mid pregnancy so any changes after were not captured 2. Details of instrument used were not provided 2. Anxiety was not assessed with reliable and valid instrument so level of anxiety was unknown	Age, race, smoking history, Medicaid Insurance, and pre-pregnancy BMI

Table 4.1 (Continued). Studies on the relationship of at least two psychological stress factors (stress, anxiety, and/or depression) with the development of a hypertensive disorder during pregnancy

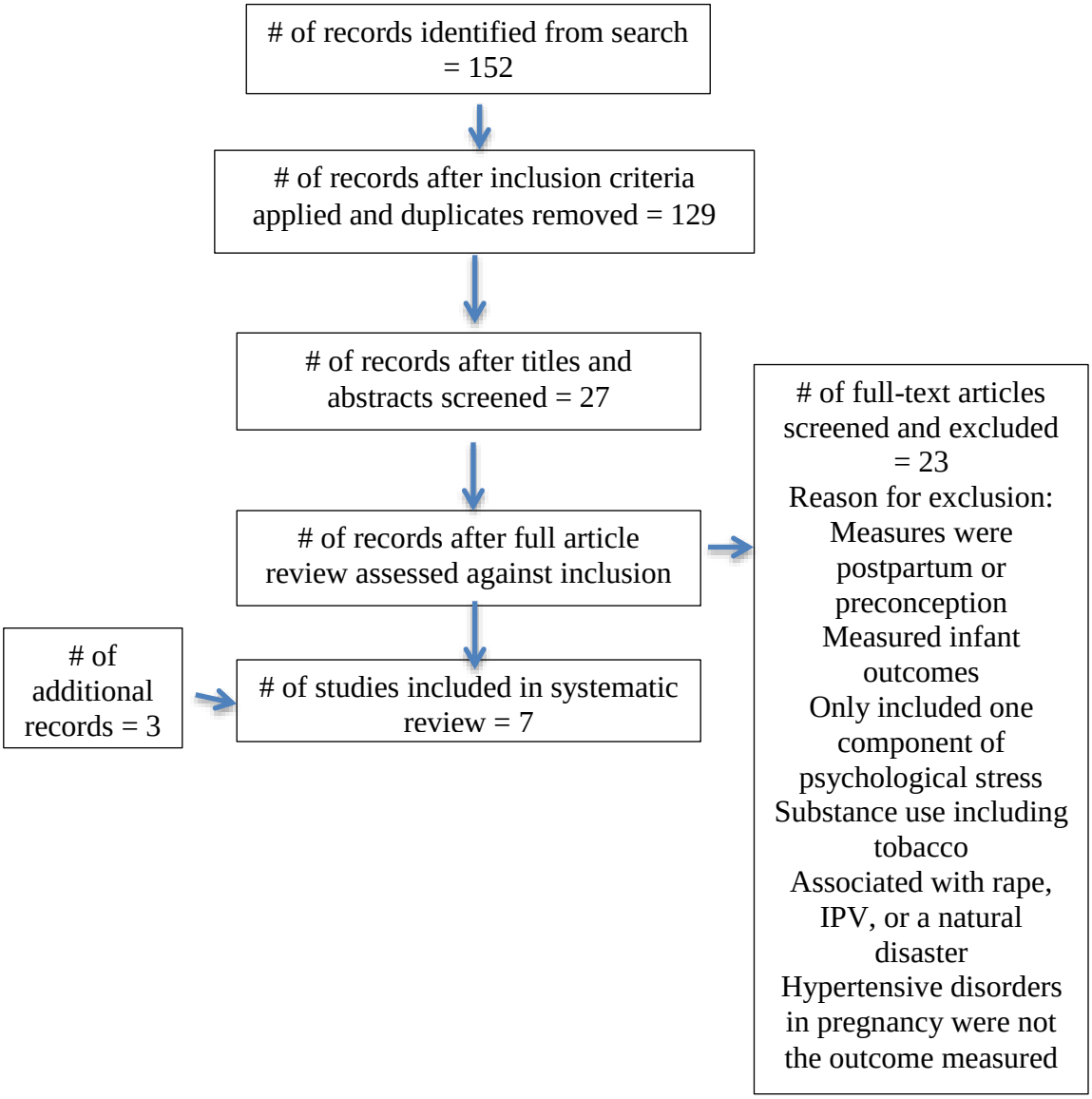
Author(s), year; Title	Setting/Design	Sample/time point of assessment	Measure(s)	Results	Strengths (Salvador-Moys et al.) and limitations (2)	Control variables
Vollebregt, K. C., van der Wal, M. F., Wolf, H., Vrijkotte, T. G. M., Boer, K., & Bonsel, G. J. (2008)	Netherlands/ prospective cohort	N = 3679; > 24 weeks gestation	Work Experience and Appreciation Questionnaire, State-Trait Anxiety Inventory, Center for Epidemiological Studies Depression Scale, and Pregnancy-related Anxiety, self-report	Workstress, anxiety, pregnancy-related anxiety or depression had no effect on the incidence of a hypertensive disorder	1. Assessed four categories of psychological disorders with well-validated questionnaires 2. Assessed in beginning of pregnancy prior to signs of preeclampsia 2. Only assessed at one time point 2. All data was self-reported	Age, marital status, pre-pregnancy BMI, chronic hypertension

Figure 4.1. PNI Framework in Pregnancy: Pathways Linking Psychological Distress, Immune Function, and Perinatal Health Outcomes



Greater exposure to objectively stressful events or stressors results in greater experience of psychological distress (A). This effect is moderated by coping resources, including social support (B). Psychological distress may affect immune function via health behaviors (C) and direct physiological pathways (D) via effects on neuroendocrine and the sympathetic nervous system. In turn, immune parameters may affect maternal health (e.g., hypertensive disorders, susceptibility to infectious illness, wound healing), birth outcomes, and fetal development (E).

Figure 4.2. Design Diagram for Articles Included in Review



Chapter V: Determining Psychological Distress During Pregnancy and Its Association with the Development of a Hypertensive Disorder

Introduction

Hypertensive disorders in pregnancy include several classifications such as chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia. These high-risk disorders complicate 5-10% of all pregnancies in the United States and are associated with increased maternal and fetal morbidity and mortality (American College of Obstetricians and Gynecologists, 2013). Maternal morbidity associated with a hypertensive disorder during pregnancy includes acute renal failure, acute liver injury, seizures, pulmonary edema, hemolysis, and thrombocytopenia (Ramma, 2011). Fetal morbidity is related to preterm birth and intrauterine growth restriction, fetal weight, and low Apgar scores (Can et al., 2011; Mihu et al., 2015).

Both normal and high-risk pregnancies are characterized by psychological and biological changes. These changes occur in each trimester of pregnancy along with the pregnant woman's response to these changes (Coussons-Read, Okun, & Nettles, 2007). Sometimes these changes are maladaptive or lead to distress and adverse birth outcomes (Roesch, Schetter, Woo, & Hobel, 2004). Psychological distress may contribute to adverse pregnancy outcomes by influencing biological factors leading to dysregulation of the maternal immune response (Lederman, 1995; Yu et al., 2013; Zhang et al., 2013). Prevalence of psychological distress in pregnancy has been reported between 13 and 25% (Çapik & Pasinlioglu, 2015) and primarily consists of stress, anxiety, and depression (Emmanuel & St John, 2010). The psychological component is often overlooked or not addressed by healthcare providers (Goodman & Tyer-Viola, 2010). Hence, it is important

to assess psychological distress throughout pregnancy and understand if psychological distress is associated with the development of a hypertensive disorder.

Researchers have not reached consensus regarding the association between psychological distress and development of a hypertensive disorder during pregnancy. Although many differences exist in study design, conceptual frameworks, timing of data collection (e.g. trimester of pregnancy), and use of different instruments to assess components of psychological distress contribute to varied results (Andersson et al., 2004; Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). The primary concern is the lack of consensus of operationalized definitions of the components of distress.

Stress and the Development of a Hypertensive Disorder

Mental stress was associated in a pooled effect with increasing the risk of preeclampsia (OR 1.49; CI 1.27 – 1.74, $p < .001$) in a meta-analysis (Zhang et al., 2013). Mental stress included work stress, job strain, pregnancy-related stress, life stress, perceived stress, and psychosocial stress. Greater perceived general lifetime stress (OR 2.1; CI 1.6 – 2.9, $p < .001$), and perceived stress during pregnancy (OR 1.7; CI 1.3 – 2.2, $p < .001$) were associated with an increased risk of a hypertensive disorder (Yu et al., 2013). In a study conducted by Vollebregt et al., the effects of stress were not detected in the beginning of pregnancy or during the development of a hypertensive disorder during pregnancy (Vollebregt et al., 2008).

Anxiety and the Development of a Hypertensive Disorder

Anxiety levels differed between women with an increased blood pressure and those without; however, differences were not specified (Franco et al., 2015). Anxiety was associated with an increased risk (OR 3.2; CI 1.4 – 7.4) for a hypertensive disorder, but a limitation was anxiety was assessed with one question (Kurki et al., 2000). Reported anxiety disorders during pregnancy were also associated with an increased risk of preeclampsia (RR = 2.12; CI 1.02 – 4.45, p = .045) in a study of women before 20 weeks gestation (Qiu et al., 2009). However, this study did not control for the use of psychotropic medications. Four prospective studies did not support anxiety symptoms with the development of a hypertensive disorder (Andersson et al., 2004; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). Furthermore, anxiety levels did not differ for those with a hypertensive disorder from those without the disorder as measured in the beginning and end of the second trimester (Sikkema et al., 2001).

Depression and the Development of a Hypertensive Disorder

Franco et al., reported a significant difference in depression levels between women with an increased blood pressure and those without but did not report how they differed (Franco et al., 2015). In a prospective study, depression was associated with an increased risk (OR 2.5; CI 1.1 – 5.4) for a hypertensive disorder (Kurki et al., 2000). However, a significant relationship was not identified in three other prospective studies (Andersson et al., 2004; Thombre et al., 2015; Vollebregt et al., 2008).

Limitations to these studies included using small sample sizes in most, assessment timing, having a cross-sectional design, and the use of different instruments to assess psychological distress. Psychological distress components were measured after symptoms

of a hypertensive disorder could appear (i.e. after 20 weeks gestation) thereby eliminating the ability to predict and possibly altering the severity of symptoms (Thombre et al., 2015; Vollebregt et al., 2008). Furthermore, the cross-sectional design of the most of these studies limited the understanding of how psychological distress changes throughout pregnancy. Sikkema et al. strengthened their study by using a longitudinal design collecting data early and late in the second trimester to capture changes in anxiety levels (Sikkema et al., 2001).

This study addresses a highly significant topic, psychological distress and the development of a hypertensive disorder. Given the severity of these disorders both maternal and fetal, understanding the etiology of hypertensive disorders is an important objective. Researchers have not paid much attention to psychological distress with respect to changes and timing throughout pregnancy in association with the development of a hypertensive disorder. Overwhelmingly, researchers have utilized a cross-sectional method rather than a longitudinal method in their studies. Furthermore, it remains unclear whether specific components of psychological distress (e.g., stress, anxiety, and depression) influence the development of a hypertensive disorder. Few studies included a comprehensive investigation of psychological distress by including stress, anxiety and depression using a conceptual framework.

Conceptual Framework

There is limited literature incorporating a conceptual framework to explain the relationship between psychological distress and a hypertensive disorder during pregnancy. The psychoneuroimmunology (PNI) framework illustrates connections between psychological distress, immunity, and pregnancy outcomes by way of the

sympathetic nervous system (SNS) and activation of the hypothalamo-pituitary-adrenal (HPA) axis (Christian, 2012; Coussons-Read et al., 2003). Perception of a stressor activates the SNS and HPA axis. This activation may put pregnancies at risk if the psychological distress is of long duration. The PNI framework will allow the researcher to test three hypotheses related to psychological distress during pregnancy and an associated with the development of a hypertensive disorder during pregnancy (Figure 5.1). I have operationalized stressors as the pressures experienced by the mother during pregnancy. The response to these stressors is psychological distress. Therefore, psychological distress is events, situations, and emotions that negatively affect one's well-being or are perceived as harmful. Additionally, the components of psychological distress (perceived stress, general anxiety, and depression) are on a continuum without distinct boundaries (Figure 5.2). Emmanuel et al. illustrated this concept with a slight variation. In a concept analysis, maternal distress was the concept. In this concept, the stressors or pressures were pregnancy-related resulting in maternal distress (Emmanuel & St John, 2010). My concept is psychological distress and, as opposed to maternal distress, it is not explicitly pregnancy-related rather psychological distress results from perceived stress, general anxiety or depression. The focus of this study will only be related to the results from stressors and not specifically what the stressors may be for that individual.

Based on the current research and limitations of those existing studies, more research is warranted. Therefore, the purpose of this study was to investigate the changes of psychological distress using validated measures such as the Perceived Stress Scale (PSS), the Generalized Anxiety Disorder (GAD) scale, and the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) assessed in pregnancy and determine if

there was an association with any component of psychological distress and the development of a hypertensive disorder using the (PNI) framework in pregnancy.

Specific Aims

Aim 1. To compare psychological distress (perceived stress, general anxiety, and depression) between women who developed a hypertensive disorder (n = 29) and those who did not (n = 87).

Hypothesis 1: Women who develop a hypertensive disorder during pregnancy will have higher perceived stress, general anxiety, and depression levels.

Aim 2. To determine whether psychological distress (perceived stress, general anxiety, and depression) measured prior to 20 weeks gestation with PSS, GAD, and CESD-R were independent predictors of a hypertensive disorder.

Hypothesis 2: Perceived stress, general anxiety, and depression measured prior to 20 weeks gestation will be independent predictors of a hypertensive disorder.

Aim 3. To compare the trajectory of psychological distress (perceived stress, general anxiety, and depression) throughout pregnancy between normotensive women and those with a hypertensive disorder

Hypothesis 3: Perceived stress, anxiety, and depression scores will be higher at the end of pregnancy for women experiencing a hypertensive disorder compared to women who do not develop the disorder.

Approach

Design

This investigation was a case-control (1:3) secondary data analysis using data collected from the EMPOWR (Efforts to Maximize Perinatal Outcomes in Women at

Risk) study (Hieronymus et al., 2016), a prospective multicenter study. Prevalence of a hypertensive disorder for this cohort was 5.4%. This prevalence is within the reported values nationwide (5-10%).

Five prenatal clinics in Central and Eastern Kentucky served as recruitment sites. Three prenatal clinic sites provided EMPOWR group prenatal care and served as collection points at 1) prior to 20 weeks gestation; 2) during the third trimester (28 weeks – birth); and 3) 2-8 weeks postpartum. All enrolled subjects were receiving Medicaid assistance and had at least one risk factor for preterm birth based on IOM, 2007 criteria (Behrman & Butler, 2007). Initially, enrolled subjects provided demographic information, reproductive and prenatal history, psychological distress and laboratory assessments, and a patient intake survey. Based upon an identified risk factor for preterm birth either obstetric/medical conditions, tobacco use or substance abuse, obesity or diabetes, Hispanic, or psychosocial variables, eligible participants were placed in a distinct group arm specifically designed to address that risk factor. Overall psychological distress assessments were collected at three time points: prior to 20 weeks gestation, after 27 weeks gestation, and postpartum.

Human subjects research protection was provided in the parent study. The EMPOWR study received approval form the University of Kentucky's Institutional Review Board (IRB). Trained research team members with experience and expertise in maternal child health as well as full group care training addressed the potential risks. Subjects did not directly benefit but received standard of care treatment. Consent and HIPAA were required. Research materials obtained from the study were stored in a locked cabinet in the College of Nursing or in locked cabinets at off-site participating

locations. Only principal investigator or research manager transported data from off-site locations. Only the principal investigator and research manager had access to all data and patient identifiers. The parent study included women and minorities. Spanish and English versions of all study materials were provided at all recruitment sites.

Sample

The inclusion criteria for the parent study consisted of pregnant women ≥ 14 years of age, less than 30 weeks gestation, on Medicaid, and demonstration of at least one risk factor for preterm birth. Women were excluded if they had a history or current diagnoses of a mental illness. Inclusion criteria for the secondary analysis will be the same as the original study and the addition of those women who developed a hypertensive disorder during pregnancy. The cases (n = 29) for this study were women who developed a hypertensive disorder during pregnancy. They were matched with controls, n = 87, on age and parity with women who did not develop a hypertensive disorder during pregnancy.

Setting

Researchers in the parent study recruited the target population from five prenatal clinics throughout Kentucky, two of which were university-based clinics. The combined projected enrollment for the three-year study was 856. The actual enrollment was 696.

Measures

Three valid self-report instruments were used to measure depression levels, anxiety levels, and perceived stress across pregnancy in the parent study.

Depression. Depression was measured with the Center for Epidemiologic Studies Depression Scale Revised (CESD-R). The CESD-R is a 10-question inventory used to

measure current level of depressive symptoms (Miller, Anton, & Townson, 2008; Radloff, 1977). Patients were asked how often during the past week they felt depressive symptoms. Response options were 'rarely or none of the time,' 'some or a little of the time,' 'occasionally or a moderate amount of time,' and 'most or all of the time.' Each response is scored from 0 to 3 on a scale of frequency of occurrence of symptoms; two of the items are reversed scored. A cumulative score is obtained by summing each item for a range from 0 – 30, with higher scores indicating more symptoms. A cut-off score of ≥10 is widely used to represent 'depressed' (Andresen, Malmgren, Carter, & Patrick, 1994).

The original CESD and CESD-R have demonstrated concurrent validity by clinical and self-report criteria and construct validity through factor analysis (Björgvinsson, Kertz, Bigda-Peyton, McCoy, & Aderka, 2013; Boey, 1999; Radloff, 1977). The CES-D has demonstrated high internal consistency with Cronbach's α 0.88 in a pregnant population (Radloff, 1977). The CESD-R has also demonstrated along high internal consistency with Cronbach's α 0.86 in patient population, and 0.92 in general population (Miller et al., 2008; Van Dam & Earleywine, 2011). Acceptable ranges for internal consistency are between 0.3 and 0.8 (Waltz, Strickland, & Lenz, 2010). Components of factor analysis included: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness.

Anxiety. Anxiety was measured with the Generalized Anxiety Disorder measure, 7-item (GAD – 7). The GAD-7 is a brief measure for assessing generalized anxiety and symptom severity (Spitzer et al., 2006). Patients are asked how often during the last two weeks they were bothered by each of the symptoms. Response options were 'not at all,' 'several days,' 'more than half the days,' and 'nearly every day.' Scores were 0, 1, 2, and

3, respectively. Summed scores range from 0 – 21 with higher scores indicated higher levels of anxiety and/or symptom severity (Spitzer et al., 2006). The GAD-7 yielded a sensitivity (true positive) of 73.3% and specificity (true negative) of 67.3% at a cut-off score of 7 in pregnancy (Zhong et al., 2015).

The internal consistency of the GAD-7 was excellent with a Cronbach's α 0.92 in a general patient population (Spitzer et al., 2006) and 0.89 in a pregnant population (Zhong et al., 2015). Validity was established with factor analysis as well as convergent validity with correlations with Beck Anxiety Inventory (r = 0.72) and the anxiety subscale of the Symptom Checklist – 90 (r = 0.74) (Spitzer et al., 2006). Convergent validity is claimed if r is above 0.70 (Waltz et al., 2010).

Stress. Stress was measured with the Perceived Stress Scale, 4-item (PSS – 4). The Perceived Stress Scale PSS is a questionnaire developed by Cohen et al. to evaluate the degree to which an individual perceives life situations as stressful. The PSS is one of the most widely used instruments for measuring stress (Lee, 2012). It has three forms, 4-item, 10-item, and 14-item all created in the early 80's (Cohen, Kamarck, & Mermelstein, 1983). The items are answered with a 5-point Likert-scale and range from 0 (never) to 4 (very often). Ranges for the PSS-4 are 0 to 16. Scores are summed and a higher score indicates greater perceived stress. The instrument was designed for use with almost any sub-population group due to the generality of the content. Questions reflect feelings an individual experienced over the past month.

Initial validation methods of PSS conducted by Cohen et al. consisted of two groups of college students and a group enrolled in a smoking cessation program (1983). Internal consistencies using Cronbach's α were 0.84, 0.85, and 0.86 in each of the

samples (Cohen et al., 1983). In addition, test-retest correlation in a sample of college students was 0.85, whereas the correlation was only 0.55 for the smoking cessation group (Cohen et al., 1983). Construct validity was assessed through correlations between the PSS and Life-Event Scores. Small to moderate correlations between the impact of life events and the PSS in college student samples 1 and 2, along with smoking-cessation groups at beginning and end of treatments were evident (0.35, 0.24, 0.49, 0.33, respectively, $p < .01$) (Cohen et al., 1983). PSS has also been used to measure subjective stress among pregnant women (Liou, Wang, & Cheng, 2014; Parcells, 2010) but only one study reported internal consistency with Cronbach's α 0.80 (Hayase, Shimada, & Seki, 2014).

Demographic Characteristics and Survey Variables

Demographic data were collected through self-report (race, parity, marital status, educational level, BMI, and tobacco use) or medical record (Wager & Jefferson) at the initial visit prior to 20 weeks gestation in the parent study.

Procedures

An exemption certification was obtained from the University of Kentucky IRB for this study as de-identified data from a data repository was used. Data were obtained and sorted to include a group of women who developed a hypertensive disorder during pregnancy. In addition, data were filtered at each trimester to account for any missing data. Andersen et al., recommends using mean imputation to replace one missing score if needed (Andresen et al., 1994). If necessary, data was transformed to obtain a normal distribution. Continuous data was used if normalizing is possible. If normalizing the data is not possible, data was categorized prior based on set cut-off points from previous

studies. Means and standard deviations were reported as original non-transformed variables.

Analysis

Descriptive statistics were used to characterize the participants in the secondary analysis. Bivariate analysis including t-test and chi-square test were used to compare between the two groups (women with a hypertensive disorder and those without) to determine whether there were differences in sociodemographic variables. Results will be reported as mean ± standard deviation or number (n) and percent (%). All analysis will be conducted with SPSS version 22 (Amonk, NY). A priori significance level is $p = 0.05$.

Aim 1**.** To compare psychological distress (perceived stress, general anxiety, and depression) between women who developed a hypertensive disorder (n = 29) and those who did not (n = 87). Comparisons of differences of means between groups were measured with independent t-tests or Mann-Whitney for nonparametric data. Results were reported as means and standard deviations.

Aims 2.To determine whether psychological distress (perceived stress, general anxiety, and depression) measured prior to 20 weeks gestation with PSS-4, GAD-7, and CESD-R were independent risk factors in the development of a hypertensive disorder. Logistic regression analysis was used to determine if the presence of depression, anxiety, or perceived stress measured early in pregnancy were risks in the development of a hypertensive disorder. Adjustments were made for the following known risk factors that influence the development of a hypertensive disorder during pregnancy: BMI, race, and smoking status (Sibai et al., 1997) and adjusted odds ratios were reported. The sample size of 116 was sufficient to meet the suggested 10-15 cases of data for each variable in

the model (Field, 2009). Assumptions in this analysis were depression, anxiety, and perceived stress were independent variables. If multicollinearity existed, adjustments were made either through measuring the interaction effect or centering each variable. If data were severely skewed, cut points were used to create dichotomous variables.

Aim 3. To compare the trajectory of psychological distress (perceived stress, general anxiety, and depression) throughout pregnancy between normotensive women and those with a hypertensive disorder. In order to assess changes over time, repeated measures ANOVA was performed to explore changes in depression, anxiety, and perceived stress as reported in the CESD-R, GAD-7, and PSS-4 instruments for those with a hypertensive disorder compared to the normotensive group.

Results

Patient Characteristics

Per study design, the sample consisted of 29 (25%) pregnant women with a hypertensive disorder and 87 (75%) without the disorder. The average age for the group was 23 years old. The majority of the sample was not Caucasian (68%). The majority, 86%, had a high school degree, equivalent, or less. More of the sample were married or living with their partner (57%) than single or not living with their partner (43%). Thirty-four percent of the sample reported smoking three months prior to pregnancy. There were no significant differences between hypertensive and normotensive demographic or social characteristics for this sample of women with the exception of BMI. In this sample, women with a hypertensive disorder had a significantly higher BMI than normotensive women. Table 5.1 provides patient characteristics of this sample.

Specific Aim 1 – Comparison of Distress Between Groups

Data were checked for normality. As the data were close to a bell-shaped curve and the sample size was sufficient, normal theory based test were used throughout the analysis. Independent t-tests compared distress scores between women who developed a hypertensive disorder in pregnancy with normotensive women. Scores measuring depressive symptoms, perceived stress, and symptoms of anxiety in early and late pregnancy were compared between groups. There were no significant differences between normotensive and hypertensive women at any of the time points. Tables 5.2 and 5.3 provide the comparisons (mean ± SD) of the two groups.

Specific Aim 2 – Independent Predictors of Developing a Hypertensive Disorder

Multivariate logistic regression was used to determine if any the study variables were independent predictors for the development of a hypertensive disorder. Prior to running the analysis, the assumptions were checked and multicollinearity was not a factor. Smoking status, race, and BMI were included as they are known to be associated in the development of a hypertensive disorder of pregnancy (Paré et al., 2014; B. D. Sibai, Gus; Kupferminc, Michael, 2005). The three variables of distress as measured by the CESD-R, PSS-4, and GAD-7 were also included to test the predictability of these factors. There was a significant association between BMI and the development of a hypertensive disorder of pregnancy. For every unit increase in BMI, there was a 13% increase in developing a hypertensive disorder. Table 5.4 illustrates the multivariate model.

Specific Aim 3 – Changes in Distress Variables by Time

Repeated measures ANOVA resulted in no significant main effects of difference over time or by hypertensive status for CESD-R, PSS-4, or GAD-7 scores. The interaction between time and hypertension was not significant in the model.

Discussion

The results of the present study do not support psychological distress as a contributing factor to the development of a hypertensive disorder during pregnancy. Depressive symptoms, perceived stress, and symptoms of anxiety were not different between groups early in pregnancy. This finding is similar to Sikkema et al., reporting no differences in State-Trait Anxiety Inventory scores between normotensive and hypertensive women (Sikkema et al., 2001). Yu et al. reported different results when assessing perceived stress during pregnancy. The researchers stated women with preeclampsia has higher levels of perceived stress during pregnancy than women without the disorder (Yu et al., 2013). Perceived stress was measured with one question differing from the PSS-4 used in this study and may have accounted for this difference. Lastly, Kim et al., reported a difference in depression symptoms as measured early in pregnancy with the Edinburgh Postnatal Depression Scale (EPDS) between a sample of African-American women with a hypertensive disorder and women without the disorder (Kim et al., 2013).

In addition, results of the present study do not suggest any component of psychological distress early in pregnancy is associated with the development of a hypertensive disorder. This finding is similar to studies (Andersson et al., 2004; Sikkema

et al., 2001; Vollebregt et al., 2008). Andersson, et al., did not find significant associations in depressive and anxiety disorders with the development of a hypertensive disorder using the Primary Care Evaluation of Mental Disorders. Vollebregt et al., did not find associations of work stress, anxiety, or depression measured early in pregnancy and the development of a hypertensive disorder later in pregnancy (Vollebregt et al., 2008). Similarly, Sikkema et al., did not support an association of anxiety with the development of preeclampsia using the State-Trait Anxiety Inventory (Sikkema et al., 2001). However, Kurki et al., reported in a study on preeclampsia a significant association between the disease and antenatal depressive and/or anxiety symptoms (Kurki et al., 2000). This difference could be due to the instruments used in assessing depressive symptoms, i.e. CESD-R in this study compared to Beck Depression Inventory and GAD-7 in this study compared to one question used to assess the presence of anxiety. Thrombre et al., also reported associations between maternal depression or anxiety symptoms and hypertensive disorders of pregnancy but these associations were driven primarily by the presence of chronic hypertension (Thombre et al., 2015).

Body mass index (BMI) was an independent predictor in the development of a hypertensive disorder. This finding has been supported in other studies. In a sample of 2637 women being overweight or obese was the most important risk factor with an adjusted odds ratio 1.65; 1.13-2.41 for BMI 25-30 (Paré et al., 2014). Furthermore, as BMI values increase above the normal weight range, they were associated with a higher likelihood of major depression in pregnancy (Bodnar, Wisner, Moses-Kolko, Sit, & Hanusa, 2009). In addition, women with a BMI above the normal weight were significantly more likely to have depression and/or anxiety compared to women with a

normal BMI (Zhao et al., 2009). Body mass index fits within the PNI framework as a health behavior that can influence the immunological response, specifically an exaggerated pro-inflammatory response. This response can thereby lead to adverse pregnancy outcomes such as the development of a hypertensive disorder of pregnancy (Ruyak & Corwin, 2013).

There were no differences by time with any component of psychological distress between women with a hypertensive disorder of pregnancy and normotensive women. Depressive symptoms, perceived stress, and symptoms of anxiety early and late in pregnancy were not different between groups. Few studies have measured maternal psychological distress over time comparing hypertensive and normotensive women. Sikkema et al. reported no differences in anxiety scores between women with a hypertensive disorder and those without the disorder at 17-18 weeks gestation or at 27-28 weeks gestation.

Limitations

Limitations for this study include being a secondary data analysis, sample size, and the presence of bias. As a secondary data analysis, the researcher has no control of the parent study sample population. The development of a hypertensive disorder was not the primary focus of the parent study; therefore, they did not screen potential participants for high risk factors for the development of a hypertensive disorder. Another limitation is the small sample size of participants that met the criteria of a hypertensive disorder. The presence of recall bias with this type of study could also be a limitation. The questionnaires used to assess psychological distress were based on participant's recollection of feelings of stress, anxiety, and depression; therefore, an inaccurate

assessment of their symptoms may have occurred. Memory errors such as forgetting result in under-reporting (Adams, Soumerai, Lomas, & Ross-Degnan, 1999). The use of self-report measures may not accurately reflect the actual level of psychological stress in part due to social desirability bias. Social desirability bias occurs when an individual reports the socially desirable behavior when questioned (Adams et al., 1999). There is a societal norm that the experience of pregnancy is a happy and joyful time in life so women experiencing psychological distress may under-report their symptoms or severity (Dunkel Schetter, 2011). Sampling bias is a systematic error in sampling procedures that can distort the results of a study. The most common type of sampling bias is non-response bias. This occurs when the people refuse to participate in a study and those non-respondents are different from those that responded and this difference is not captured (World Health Organization, 2014). The parent study projected a 25% enrollment rate indicating a 75% non-response rate. If there are differences between these two groups, study results will not generalizable outside of the study population.

Future Research

Future research should consider the use of prospective, longitudinal studies with large sample sizes using a conceptual framework, valid instruments and a biological measure. The PNI Framework in Pregnancy can serve as a model for future studies. Using the PNI Framework in Pregnancy, stressors can be evaluated as well as determining the mediating effects of coping mechanisms to identify areas where nursing interventions could provide the most influence. For example, after evaluating a stressor, nurses or healthcare providers could assist the pregnant mother to identify sources of social support thereby possibly reducing the psychological distress. Another example

would be in identifying the psychological distress and help the pregnant woman modify health behaviors such as diet and sleep. The PNI Framework allows for assessments of stressors, coping mechanisms, psychological distress responses, modifiable behaviors associated with these psychological distress responses, and the effects on inflammatory response and/or maternal outcomes such as the development of a hypertensive disorder during pregnancy. In addition to evaluating psychological distress during pregnancy with self-report measures, the use of a biomarker confirmation of stress, anxiety, and depression would strengthen the reliability of the findings. These methods should be included in future studies.

Conclusion

This was one of the first longitudinal studies thoroughly evaluating the components of psychological distress using valid instruments and a theoretical framework. The framework provided a foundation to test three hypotheses. In this population, they hypotheses tested were not supported and psychological distress was not different between women with a hypertensive disorder of pregnancy and those without the disorder. Furthermore, psychological distress did not differ early or late in pregnancy between these two groups. Women in both groups reported having some depressive symptoms, and fewer symptoms of anxiety or perceived stress. In addition, the components of psychological distress were not independently associated with the development of a hypertensive disorder of pregnancy. This study did compliment other evidence reporting BMI as an independent risk factor in the development of a hypertensive disorder during pregnancy.

Investigating these modifiable risk factors in the development of a hypertensive disorder should continue to be a research priority. Longitudinal research studies with larger sample sizes and using the PNI framework is warranted in order to better understand the role of these variables in the development of this adverse pregnancy outcome.

Table 5.1. Sample characteristics of women with a hypertensive disorder compared to normotensive women (n = 116)

Characteristic	Hypertensive Disorder	Normotensive	p-value
Age; mean ± SD	23 ± 5.4	22.7 ± 5.6	.793
BMI; mean ± SD	31 ± 1.7	27 ± 0.8	.019*
Race Caucasian; n, % Not Caucasian; n, %	 12 (41.4%) 17 (58.6%)	 25 (28.7%) 62 (71.3%)	.251
Education High school or less; n, % Greater than high school; n, %	 22 (75.9%) 7 (24.1%)	 78 (90.7%) 8 (9.3%)	.134
Relationship Status Single/not living with partner; n, % Married/living with partner; n, %	 13 (44.8%) 16 (55.2%)	 37 (42.5%) 50 (57.5%)	.819
Smoking Status 3 mo. prior to pregnancy Yes; n, %	5 (21.7%)	34 (39.5%)	.145

*significant to ≤ .05

Table 5.2. Comparison of distress scores between normotensive women and women with a hypertensive disorder of pregnancy early in pregnancy

Measure of Distress	Hypertensive (n = 29)	Normotensive (n = 87)	p-value
CESD-R (mean ± SD)	10.78 ± 6.81	10.55 ± 7.62	.885
PSS-4 (mean ± SD)	5.61 ± 2.56	5.31 ± 3.20	.654
GAD-7 (mean ± SD)	5.75 ± 4.93	5.32 ± 4.71	.679

Table 5.3. Comparison of distress scores between normotensive women and women with a hypertensive disorder of pregnancy late in pregnancy

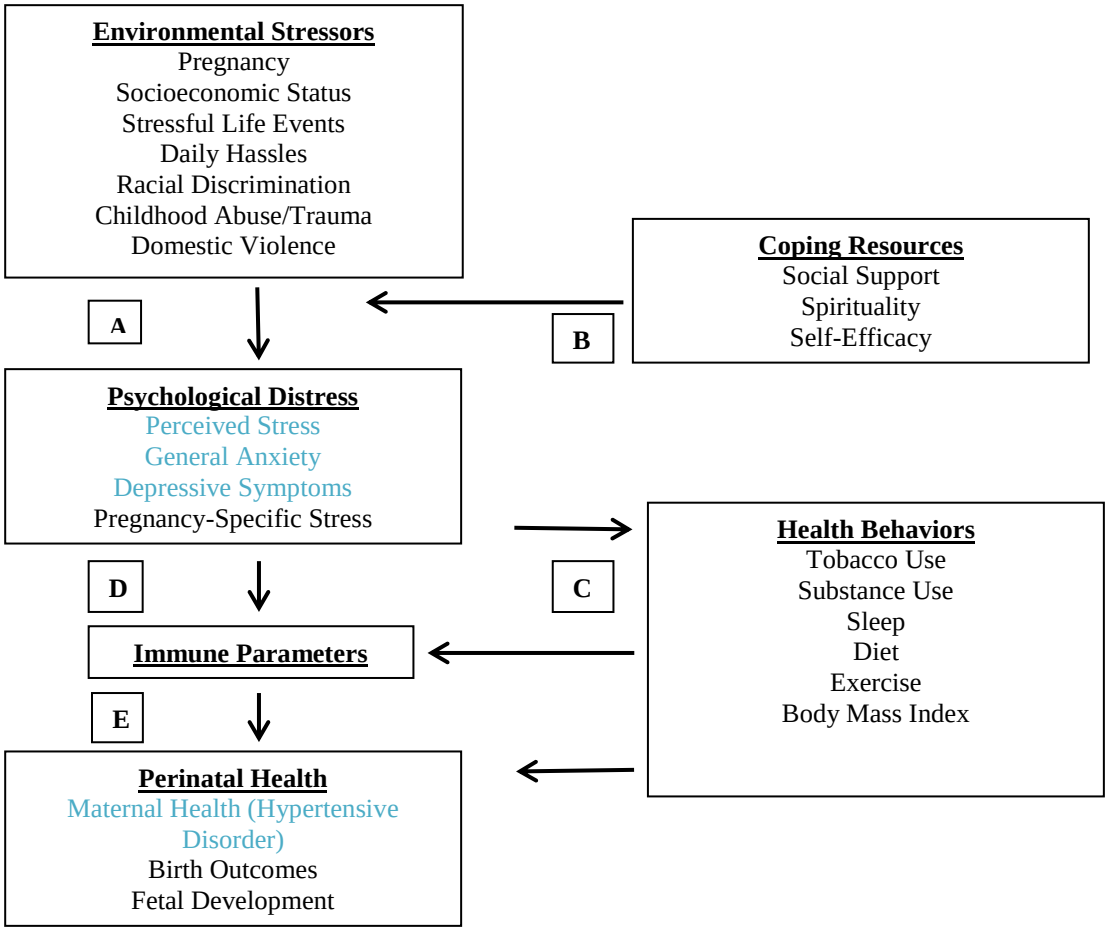
Measure of Distress	Hypertensive (n = 16)	Normotensive (n = 45)	p-value
CESD-R (mean ± SD)	9.74 ± 7.08	10.59 ± 8.03	.709
PSS-4 (mean ± SD)	5.88 ± 2.78	5.80 ± 3.23	.935
GAD-7 (mean ± SD)	5.12 ± 4.46	5.67 ± 5.14	.699

Table 5.4. Multivariate model for development of a hypertensive disorder of pregnancy

	Odds Ratio	95% Confidence Interval	p-value
CESD-R	.888	.763 - 1.033	.125
PSS-4	1.240	.915 - 1.680	.165
GAD-7	1.171	.958 - 1.433	.123
Smoking	.504	.116 - 2.182	.360
Race	1.449	.347 - 6.044	.611
BMI	1.131	1.042 - 1.229	.003*

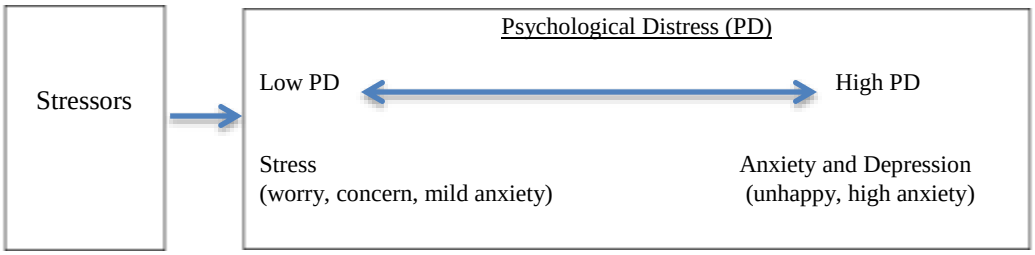
*significance to ≤ .05

Figure 5.1. PNI Framework in Pregnancy: Pathways Linking Psychological Distress, Immune Function, and Perinatal Health Outcomes



Greater exposure to objectively stressful events or stressors results in greater experience of psychological distress (A). This effect is moderated by coping resources, including social support (B). Psychological distress may affect immune function via health behaviors (C) and direct physiological pathways (D) via effects on neuroendocrine and the sympathetic nervous system. In turn, immune parameters may affect maternal health (e.g., hypertensive disorders, susceptibility to infectious illness, wound healing), birth outcomes, and fetal development (E).

Figure 5.2. Concept of Psychological Distress on a Continuum



Chapter VI: Conclusions and Discussions

Synthesis of Findings and Implications

The purposes of this dissertation were to: 1) understand the experience of having a hypertensive disorder during pregnancy; 2) to investigate the association of perceived stress and changes in immune response via biomarker measures in women who develop a hypertensive disorder during pregnancy; 3) to review, summarize, and evaluate the literature examining the relationship between perceived maternal distress (stress, anxiety, and depression) and the development of a hypertensive disorder; and 4) to investigate the association of perceived distress in the development of a hypertensive disorder during pregnancy. In this dissertation, four studies were presented. The first was a qualitative descriptive design used to provide a comprehensive summary of the experience of being placed on bed rest for a hypertensive disorder, specifically preeclampsia and to identify the key stressors these women experienced. Seven women met the inclusion criteria for this study. After transcription, three members of the research team performed qualitative content analysis. The team reached consensus with six themes emerging related to the stressors experienced by these women in this study. The stressors included negative thoughts and feelings, lack of guidelines and/or knowledge about their diagnosis, family stressors, lack of social support, not being heard, loss of normal pregnancy, and physical symptoms. However, the three most common stressors identified by these women were negative feelings, frustration with lack of guidelines related to diagnosis, and feelings of not being heard by their healthcare providers.

All of the study participants described negative thoughts and feelings related to their experience of preeclampsia and being placed on bed rest. Some of these negative

feelings could be characterized as anxiety related symptoms. Participants used terms such as “nervous wreck” and “stressed out” to describe their experience.

Participants also described feelings of frustration when dealing with their healthcare providers and the lack of evidence-based guidelines being used by their providers. They received “mixed messages” and their care lacked continuity between providers. The majority of these participants were actively educating themselves about their condition along with recommended treatments. Their self-education often was in conflict with the management of their high-risk condition.

Lastly, these women did not feel heard by their providers. All but one of the women in this study reported never being asked how they felt about their high-risk condition or about being placed on bed rest. When they did try to communicate with their providers about concerns or questions, they were “brushed off”. These feelings can hinder the patient-provider relationship. This is reflected in the fact that six of the seven women did not report a positive relationship with their provider. Interventional research should focus on improving psychosocial wellness during a high-risk pregnancy.

In the second study, the author explored the association of everyday stress and inflammatory response with the development of a hypertensive disorder during pregnancy. This was a secondary data analysis of a longitudinal, repeated measures, multicenter study of healthy pregnant women. Data collected from the parent study were matched on age and parity in a 1:2 case control design. Cases consisted of women diagnosed with a hypertensive disorder during pregnancy (n = 33), while controls consisted of women without a hypertensive disorder (n = 64). Prenatal stress was measured through the ESI and systemic inflammation was measured using serum

inflammatory biomarkers including both pro- and anti-inflammatory cytokines. High levels of stress altered inflammatory response in each trimester of pregnancy in both women with a hypertensive disorder and those without the disorder.

Repeated measures models showed significant main effects of stress level (high/low) and hypertension status for IL-8. Serum levels of IL-8 were reduced in those with high stress compared to women with low stress. In addition, there was an interaction effect of stress level by trimester for IL-1α. Women with high stress had lower levels of IL-1α in the first trimester compared to women with low stress in the same trimester. Lastly, a significant difference in the change of serum IL-10 levels was identified with the interaction effect of stress level and a having a hypertensive disorder by trimester. Third trimester serum levels of IL-10 were significantly higher in women with high stress and a hypertensive disorder compared to normotensive women with low stress levels.

Previous research has supported alterations in maternal inflammatory response in women with a hypertensive disorder during pregnancy. Increased serum cytokines IL-6, IL-1α, IL-1β, and IL-8 have been reported in late pregnancy (Ramma, 2011; Szarka et al., 2010). However, the current research did not support this association.

Research has also supported alterations in maternal inflammatory response associated with psychological stress, specifically high stress was associated with higher levels of serum inflammatory markers (Coussons-Read et al., 2007). However, the finding of this study did not support prior research. Women with low stress scores had higher levels of inflammatory markers than women with high stress in this study.

Lastly, women experiencing a hypertensive disorder and high levels of stress had higher levels of serum IL-6 in all trimesters. This was a similar finding to Coussons-Read

et al. (2005). Serum levels of IL-10, an anti-inflammatory marker, were significantly higher in the third trimester in women with high stress and a hypertensive disorder. This could be a compensatory mechanism. Additional research is needed to better understand the maladaptation of the maternal immune response in the presence of a heightened stress response and a hypertensive disorder during pregnancy.

The third study was a critical examination of current literature that studied the relationships of psychological distress (stress, anxiety, and depression) with the development of a hypertensive disorder during pregnancy. Seven English-language, peer-reviewed articles published between January 2008 and 2016 met inclusion criteria for review. From this review, findings with respect to an association between psychological distress and a hypertensive disorder were mixed. For example, significant positive associations were reported between a measure of psychological distress and the development of a hypertensive disorder during pregnancy in three of the reviewed studies (Franco et al., 2015; Kurki et al., 2000; Qiu et al., 2009). While other researchers did not support this finding (Andersson et al., 2004; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). Gaps were discovered with respect to the role of psychological distress in the development of a hypertensive disorder during pregnancy primarily in study design, use of conceptual framework, and instruments utilized. Future studies should be longitudinal in design, utilize a conceptual framework, and include the use of valid instruments to obtain a thorough assessment of psychological distress along with an accompanying biological measure.

The fourth study examined the association of psychological distress with the development of a hypertensive disorder during pregnancy using the PNI framework

(Christian, 2012b). This investigation was a case-control (1:3) secondary data analysis. Data was collected from a prospective, longitudinal multicenter study of women receiving Medicaid with at least one risk factor for preterm birth and without a history of mental illness (Hieronymus et al., 2016). Data collected for the secondary study was frequency matched on age and parity resulting in 29 cases of women who developed a hypertensive disorder during pregnancy and 87 women who did not develop the disorder. Psychological distress (stress, anxiety, and depression) was measured twice during pregnancy (early and late) using valid instruments. The CESD-R assessed maternal levels of depressive symptoms. Symptoms of maternal anxiety were assessed using the GAD-7 and perceived stress was assessed using the PSS-4.

In this sample there were no differences between hypertensive and normotensive demographic or social characteristics with the exception of BMI. Women with a hypertensive disorder had a significantly higher BMI than normotensive women at baseline. Furthermore, contrary to hypothesized differences, there were no differences in depressive symptoms, perceived stress, or symptoms of anxiety between these groups at any time point. This finding is consistent with Sikkema et al., with no differences reported in anxiety scores, but varies from Yu et al., reporting higher levels of perceived stress in women with preeclampsia and Kim et al., reporting higher levels of depressive symptoms in women with a hypertensive disorder (Kim et al., 2013; Sikkema et al., 2001; Yu et al., 2013).

Multivariate logistic regression examined the hypothesized independent influence of the variables psychological distress in the development of a hypertensive disorder during pregnancy. While none of the psychological distress variables were predictive in

development of a hypertensive disorder during pregnancy, BMI was significantly associated. For every unit increase in BMI, there was a 13% increase in the odds of developing a hypertensive disorder. This finding related to psychological is consistent with other studies (Andersson et al., 2004; Sikkema et al., 2001; Vollebregt et al., 2008) but differed with others (Kurki et al., 2000; Thombre et al., 2015). Anderson et al., did not find associations in depressive or anxiety disorders with the development of a hypertensive disorder (Andersson et al., 2004). Work stress measured early in pregnancy were not associated with the development of a hypertensive disorder (Vollebregt et al., 2008). Anxiety was not associated with preeclampsia in two studies, but was supported in two others (Kurki et al., 2000; Sikkema et al., 2001; Thombre et al., 2015; Vollebregt et al., 2008). Kurki et al., and Thombre et al., reported associations with depression and the development of a hypertensive disorder, while Vollebregt et al., did not find an association (Kurki et al., 2000; Thombre et al., 2015; Vollebregt et al., 2008).

Body mass index as an independent predictor in the development of a hypertensive disorder has been supported. Not only do overweight and obese women have a 35% greater risk of developing of a hypertensive disorder, they are more likely to have depression and/or anxiety symptoms compared to women with a normal BMI (Paré et al., 2014; Zhao et al., 2009).

Repeated measures ANOVA examined the hypothesized changes in trajectory of psychological distress throughout pregnancy for women with a hypertensive disorder during pregnancy. However, in this sample the hypothesis was not supported. There were no significant differences over time and the interaction between time and hypertension was not different between these groups. Currently, studies have not reported on the

interaction between time and hypertension. Sikkema et al., reported no differences in anxiety scores between women with a hypertensive disorder and those without at two different time points; one early and one in mid-pregnancy (Sikkema et al., 2001). Further longitudinal research is warranted to understand the relationship of psychological distress and a hypertensive disorder over time in pregnancy.

Suggestions for Future Research

Few studies assess psychological components and/or biological components throughout a pregnancy. This is one of the first studies to explore the components of psychological distress and biological changes throughout pregnancy.

The continued use of a framework such as the PNI framework in pregnancy is recommended. In addition to the inclusion of psychological distress components altering maternal immune response and influencing prenatal outcomes, it also includes such potential study variables as stressors, coping resources and health behaviors (Christian, 2012b). Studies could focus on the various components of the model to better understand the psychological as well as physiological changes women may undergo during pregnancy that lead to high-risk pregnancies and poor birth outcomes. Future research should utilize self-report measures of stress, anxiety, and depressive symptoms with biomarker confirmation. They should be longitudinal in design and incorporate large sample sizes due to the low prevalence of hypertensive disorders in pregnancy.

Implications for clinical practice are evident as well. Since increased BMI is a known risk factor in the development of a hypertensive disorder during pregnancy and was supported in this study, it is important healthcare providers assess maternal BMI and address this modifiable risk factor in these patients. Furthermore, although study findings

did not support the association of psychological distress (stress, anxiety, and depression) in the development of a hypertensive disorder, women having the disorder can experience symptoms of distress. Care for these women can be improved if healthcare providers assess and manage psychological wellness throughout pregnancy.

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Vita
Stephanie Kehler, BSN

Education

Institution	Degree	Date Conferred	Field(s) of Study
Western Michigan University	BSME	1994, December	Mechanical Engineering
University of Kentucky	BSN	2013, May	Nursing

Certifications and Licensure

Kentucky RN license
Current CPR/AED Certification by the American Heart Association
Certificate of Teaching and Learning

Professional Experience

Dates	Institution and Location	Clinical Position
August 2016-present	University of Kentucky, College of Nursing, Lexington, KY	Clinical Instructor
July 2013-2015	University of Kentucky Good Samaritan Hospital, Lexington, KY	Intensive Care Nurse

Dates	Institution and Location	Academic Position
January 2017 – present	University of Kentucky, College of Nursing, Lexington, KY	Simulation Instructor
August 2016 – Dec. 2016	University of Kentucky, College of Nursing, Lexington, KY	Teaching Practicum, NUR 101
August 2015-Dec. 2016	University of Kentucky, College of Nursing, Lexington, KY	Research Assistant
August 2015-2016	University of Kentucky, College of Nursing Lexington, KY	Teaching Assistant

Awards and Honors

Jonas Nurse Scholars Program 2016-2018
Recipient of Delta Psi Chapter of Sigma Theta Tau Award in 2016
Recipient of Karen Hall Sexton Scholarship Award for 2015, 2016
Recipient of UK HealthCare's Nursing Educational Award for 2012
UK CON Student Scholarship Showcase poster presentation first place winner

Research Presentations

February, 2017	**Kehler, S.,** Wiggins, A., McCubbin, A., Barnett, J., Ashford, K**.** The Association of maternal stress and immune response with development of a hypertensive disorder during pregnancy. Southern Nursing Research Society (poster)
February, 2016	**Kehler, S.**, Wiggins, A., McCubbin, A., Barnett, J., Ashford, K. Impact of prenatal tobacco use and immune response in the development of hypertensive disorders. Southern Nursing Research Society (poster)
August, 2014	Anane, A., **Kehler, S.**, Morgan, M., Norkus, K., Slone, S., Troyer, C., Zavalza-Neeson, L., Nurse awareness of blood glucose and insulin management. BSN Residency (presentation)
April, 2012	**Kehler, S**., Ashford, K., McCubbin, A., & Westneat, S., Examining the impact of prenatal stress and anxiety in women experiencing unplanned pregnancies. Student Scholarship Showcase (poster)
February, 2012	**Kehler, S**., Ashford, K., McCubbin, A., & Westneat, S., Examining the impact of prenatal stress in women experiencing unplanned pregnancies. Southern Nursing Research Society (poster)

Publications

May, 2016	**Kehler, S**., Ashford, K., Cho, M., & Dekker, R., The experience of preeclampsia and bed rest: Mental health implications. *Issues in Mental Health Nursing* (in print)
April, 2016	**Kehler, S.**, & Hahn, E., A policy analysis of smoke-free legislation in Kentucky. *Policy, Politics, & Nursing Practice* (in print)
June, 2013	Ashford, K**.,** Barnett, J., McCubbin, A., **Kehler, S**., Westneat, S. (2013). Prenatal systemic immune response in smoking and nonsmoking women. 2013 AWHONN Annual Convention. Nashville, TN. (abstract)

Professional Memberships

American Nurses Association August 2016 - present
Sigma Theta Tau member February 2013 - present

Professional Service

September, 2014 – December 2015	Critical Care Council Co-Chair, UK HealthCare Chandler Hospital, Lexington, KY

Academic Service

Teaching

Spring, 2017	Guest Lecturer – Pathophysiology/Pharmacology NUR210, University of Kentucky, College of Nursing, Lexington, KY
Fall, 2016	Guest Lecturer – Pathophysiology/Pharmacology NUR210, October 12, December 8, University of Kentucky, College of Nursing, Lexington, KY
Fall, 2013	Guest Lecturer – Pathophysiology/Pharmacology NUR870, March 2013, and October 2013, University of Kentucky, College of Nursing, Lexington, KY

Academic Service

Dates	Committee Name	Role
October, 2014-present	GNSA	Member
September, 2014-May, 2015	PhD Committee, University of Kentucky, College of Nursing, Lexington, KY	Student representative

Community Service

Spring, 2016 - present	Fundraising committee member, Paul Laurence Dunbar Band, Lexington, KY
Fall, 2015 - 2016	Fundraising committee member, Paul Laurence Dunbar Men's Soccer, Lexington, KY