2019

The Role of Psychosocial and Health Behavioral Factors in Pregnancy Induced Hypertension

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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July 2019

Acknowledgements

I am forever thankful to Dr. Saba W. Masho, my initial adviser, who encouraged me to pursue the PhD study and showed me her unconditional support and love. I would also like to express my sincerest gratitude to Dr. Tilahun Adera and Dr. Juan Lu for guiding and supporting me through my difficult time after the passing away of my initial adviser, Dr. Masho. I am further grateful to Dr. Adera for taking up the role of my primary adviser. I am also sincerely thankful to rest of the members of my committee, Dr. Robert Perera, and Dr. Edward Springel, for their sage advice and guidance. And finally, my wonderful husband, two beautiful children, and my loving parents; without your support and love, I would have not been able to come this far.

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List of Abbreviations

ACOG - America College of Obstetricians and Gynecologists
AOR – Adjusted Odds Ratio
APNCU - Adequacy of Prenatal Care Utilization
BMI – Body Mass Index
CDC- Centers for Disease Control and Prevention
CFI - Comparative Fit Index
CI – Confidence Interval
COR – Crude Odds Ratio
DAG – Direct Acyclic Graph
HEELP - Hemolysis, Elevated Liver Enzymes and Low Platelet Count Syndrome
IPV- Intimate Partner Violence
IUGR - Intra-Uterine Growth Retardation
NHANES - National Health and Nutrition Examination Survey
PIH - Pregnancy Induced Hypertension
PNC- Prenatal Care
PRAMS - Pregnancy Risk Assessment Monitoring System
RMSEA - Root Mean Square Error of Approximation
SE – Standard Error
SEM- structural equation modeling
SES – Socioeconomic Status
VIF – Variance Inflation Factor
WISE – Women's Ischemia Syndrome Evaluation

Abstract

THE ROLE OF PSYCHOSOCIAL AND HEALTH BEHAVIORAL FACTORS IN PREGNANCY INDUCED HYPERTENSION

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Background: Pregnancy induced hypertension (PIH) is the leading cause of maternal mortality and a major contributor to preterm birth and neonatal mortality. Literature suggests that several modifiable psychosocial and health behavioral factors may play significant roles in the development of PIH. However, interrelationships among these factors and their collective impact on PIH are not well understood.

Objectives: This study aims to: 1) Examine the relationship between pre-pregnancy physical activity and risk of PIH, 2) Determine the association between prepregnancy depression and PIH and the role of race/ethnicity in this association, 3) Evaluate the association between intimate

partner violence (IPV) in women before and/or during pregnancy and PIH, and the role of utilization of prenatal care (PNC) as a mediator in this association.

Methods: This study utilized the national Pregnancy Risk Assessment Monitoring System survey data (years 2009-2015). The outcome variable PIH was defined as a dichotomized variable (Yes; No) utilizing a birth certificate variable data. Domain-adjusted multiple logistic regression, multiple logistic regression with stratification, and structural equation modeling analyses were used to investigate the study aims.

Results: No significant reduced risk of PIH was observed in women who were physically active prior to pregnancy compared to sedentary women. However, women with prepregnancy depression were more likely to have PIH compared to women without prepregnancy depression and this association was significant for non-Hispanic White women when stratified by race/ethnicity. Further, PNC utilization was a significant mediator in the association between IPV before and/or during pregnancy and PIH. However, IPV had no direct or total effect on PIH in this study.

Conclusions: Public health professionals and health care providers should be aware of the relationships between prepregnancy depression, race/ethnicity, IPV, and prenatal care utilization, and PIH, and utilize the information in risk profiling, screening, early detection and intervention in women at risk of PIH.

Chapter 1: Background

Pregnancy induced hypertension (PIH), a clinically challenging group of pregnancy complications, is responsible for a substantial burden of morbidity and mortality to both mother and child. It is defined as systolic blood pressure greater than140 mmHg and diastolic blood pressure greater than 90 mmHg that develops during pregnancy.[1] The PIH refers to one of four conditions: a) gestational hypertension, b) preeclampsia c) eclampsia, and d) unclassifiable hypertension.[1,2] Gestational hypertension is the most prevalent form of PIH and is defined as a new onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at or after 20 weeks of gestation in the absence of proteinuria (<300 mg in 24 hours) or new signs of end-organ dysfunction.[2] Preeclampsia is diagnosed as gestational hypertension in association with proteinuria, thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema, or new onset cerebral or visual distrurbances.[19(2)] Eclampsia is the more severe form of PIH and is manifested by convulsion in association with other symptoms.[2] PIH complicates 5-10% of all pregnancies in the U.S.[3,4,5] and has been shown to impact both end organ complications of the mother and direct fetal complications.[5] Women with PIH are at a higher risk of adverse pregnancy outcomes such as premature delivery, intra-uterine growth retardation (IUGR), low birth weight, abruptio placentae, and intra-uterine death compared to women without PIH.[6,7] In addition, PIH can progress to complicate the pregnancy further by impairing kidney and liver function, causing blood clotting problems, pulmonary edema, and seizures, and affecting blood flow to the placenta.[2,8,9] A World Health Organization review identified hypertension as the single leading cause of maternal mortality in industrialized countries, accounting for 16% of deaths.[10] Moreover, the estimated additional cost per delivery complicated by PIH can be up to $70,100 and lifetime medical costs due to high rates of preterm

births and developmental disabilities associated with PIH was estimated at $38,250 per child annually.[11]

The incidence of PIH has increased significantly in the U.S. In last two decades, the incidence of preeclampsia has increased by 25% and gestational hypertension by 184%.[12] The rise in PIH has serious health consequences for the expectant mother and fetus, along with financial ramification on the U. S. health care system.[11,13,14] However, the reasons for this rise are not well understood. Changes in a woman's lifestyle and characteristics altering certain psychosocial and behavioral factors may have contributed to the rise of PIH. Even though the exact cause of PIH remains unknown, it is hypothesized that causation of PIH is multifactorial.[15] A social determinants of health approach to PIH can help the reserachers, health care professionals, and policymakers to identify the interrelationship between certain modifiable psychosocial and behavioral risk factors and to determine the entry points and levels of intervention based on those social determinants of health.

Etiology, Pathophysiology and Epidemiology of Pregnancy Induced Hypertension

The exact etiology of PIH remains unknown. It is thought that insulin resistance may mediate the clinical onset of hypertension in pregnancy.[16] Blood pressure is usually elevated in pregnancy due to upregulation of the renin-angiotensin-aldosterone system.[17] Whereas in healthy pregnant women this is balanced by a drop in the systemic vascular resistance, in women with gestational hypertension systematic vascular resistance remains low but cardiac output tends to increase.[17] Gestational hypertension is more common in twin pregnancies than in singleton pregnancies.[18] Healthy nulliparous women may experience higher rates of PIH (6% to 17%) compared with multiparous women (2% to 4%).[19-21] African-American women may be at greater risk than white women.[22,23] Other risk factors for PIH include extreme maternal age (<20 or >40

years old), preexisting hypertension or previous episodes of preeclampsia or PIH and preexisting renal disease.[24,25]

Significance of the current study

Pregnancy Induced Hypertension can progress very abruptly, jeopardizing the life of the mother and the fetus. Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity and a risk factor for future cardiovascular disease and metabolic disease in women in the U.S. and worldwide.[2] Further, PIH is the major contributor to prematurity.[2] These adverse outcomes can be prevented or ameliorated through early detection and intervention among the high risk population. Therefore, it is of uttermost importance to identify the population who are at risk of developing PIH and to intervene as early as possible.

The current research will aid in identifying the population at risk for PIH more effectively and promptly based on certain modifiable psychosocial and behavioral factors. For example, prepregnancy overweight/obesity, hypertension, diabetes, and cardiovascular diseases are all known risk factors for PIH [26-28] and physical inactivity is a known modifiable risk factor for obesity, hypertension, diabetes, and cardiovascular diseases [29,30] therefore, could be a potential risk factor for PIH as well. Further, women of reproductive age are at high risk for depression [31,32] and depression may contribute to pathogenesis of hypertension in these women.[33,34] Pre-existing hypertension increases the risk of PIH [29,30] thus, prepregnancy depression might be a potential risk factor for PIH. Also, an estimated 3% to 9% of pregnant women in the U.S. experience severe physical violence by an intimate partner[35,36] and intimate partner violence (IPV) around the time of pregnancy poses additional risks for poor maternal health and pregnancy outcomes.[37-40] IPV around the time of pregnancy may reduce the utilization of prenatal care by the abused women [41] and thereby, may increase the risk of PIH for these women.

Being able to identify the women susceptible to developing PIH based on these modifiable psychosocial and behavioral risk factors would enable clinicians and health professionals to effectively monitor, promptly intervene, and prevent complications related to PIH. In effort to identify women with elevated risk of developing PIH, enquiry about prepregnancy physical inactivity, prepregnancy depression, IPV before and during pregnancy, and utilization of prenatal care could be emphasized. Early detection of at-risk population and early diagnosis of PIH based on the identified risk factors will trigger prompt medical management, and halt progression towards more detrimental maternal and neonatal outcomes such as pregnancy related maternal deaths, pre-term birth and neonatal mortality.

Furthermore, in the continuous search for the etiology of PIH, this information will add important knowledge in better understanding the interrelationship between these psychosocial and behavioral factors and their role in the development of PIH and guide future research. The rising rates of risk factors, such as physical inactivity leading to obesity, prepregnancy depression, IPV around the time of pregnancy, and inadequate utilization of prenatal care might have led to an increase in the rate of PIH in the U. S. Appropriate identification and management of these amenable risk factors can reduce the health impact and societal and cost burden of complications associated with PIH. A social determinants of health approach to PIH can help the analyst, health care professionals, and policymakers in early detection of at-risk population and early diagnosis of PIH based on the identified risk factors.

Conceptual framework

The conceptual framework of the current study is based on the Commission on Social Determinants of Health framework by the World Health Organization (Figure 1-1).[42] Increasing evidence suggests that health outcomes are profoundly shaped not just by biological factors but

also by the social, economic, and cultural environment. Accordingly, PIH may be a product of interplay between multiple factors at different levels of social determinants of health, rather than just an individual biologic factor (Figure 1-1 & 1-S1). The framework differentiates "distal/structural determinants", which include all political and social factors and "intermediary determinants", a set of underlying social determinants of health on the pathway from root causes to observed inequities in health, which include behavioral, psychosocial, and biological factors, and healthcare system.[42] Interactions between structural and intermediary determinants then result in differentiations in health and wellbeing. The sequence of outcomes is most directly influenced by six sets of intermediate determinants: family-influence; health and reproductive status; health behavior, psychosocial status, access to health services; and use of health services.

The framework suggests that interrelationship between socioeconomic and political factors such as poor health policy, low SES, female gender, and minority race/ethnicity; family-influence factors such as unmarried status, low family support, and poor decision making; health and reproductive factors such as nulliparity, extreme age, and chronic diseases; health behaviors such as smoking and physician inactivity; and psychosocial factors such as stress, depression and IPV; can contribute to increase risk for PIH. Addressing each of these levels is necessary for a comprehensive social determinants approach to this maternal health issue.

This framework allows comprehension of an overall picture of social determinants of health approach to PIH by identifying the interrelationship between the above mentioned psychosocial and behavioral risk factors. Knowledge about the interrelationship among these factors in the development of PIH is needed for early detection of the at-risk population. Knowledge is also needed to establish effective interventions based on social determinants of

health approach targeting the most effective amendable risk factors and for early diagnosis and management of PIH.

Objectives

The goal of this dissertation was to examine the interrelationship between prepregnancy physical activity, prepregnancy depression, race/ethnicity, IPV, and utilization of prenatal care, and PIH. The research was conducted using the national Pregnancy Risk Assessment Monitoring System (PRAMS) for years 2009-2015 (phase 6 & 7). Specifically, this research was designed as follow:

Aim 1. To examine pre-pregnancy physical activity and the risk of pregnancy induced hypertension. We hypothesized that women who were physically active prior to pregnancy were less likely to develop PIH.

Aim 2. To determine the association between prepregnancy depression and PIH and the role of race/ethnicity in this association. We hypothesized that women with history of prepregnancy depression would have a higher likelihood of PIH compared to women with no such history and this association would vary significantly by race/ethnicity.

Aim 3. To evaluate the association between IPV in women before and/or during pregnancy and PIH, and the role of utilization of prenatal care as mediator in this association. We hypothesized that history of IPV around the time of pregnancy would reduce utilization of prenatal care and inadequate utilization of prenatal care would increase the likelihood of PIH.

Knowledge gained from the proposed research will have clinical and policy application addressing the important role of various psychosocial and health behavioral factors in early detection of risk population for and early diagnosis of PIH. The current research will aid in identifying the risk population for PIH more effectively and promptly, based on certain

modifiable psychosocial and health behavioral factors. Early detection of risk population will prompt to prevention of PIH through proper intervention targeting these modifiable risk factors at preconception period. Further, early diagnosis of PIH based on these risk factors will trigger prompt management; thus will halt further progression to more detrimental maternal and fetal outcomes.

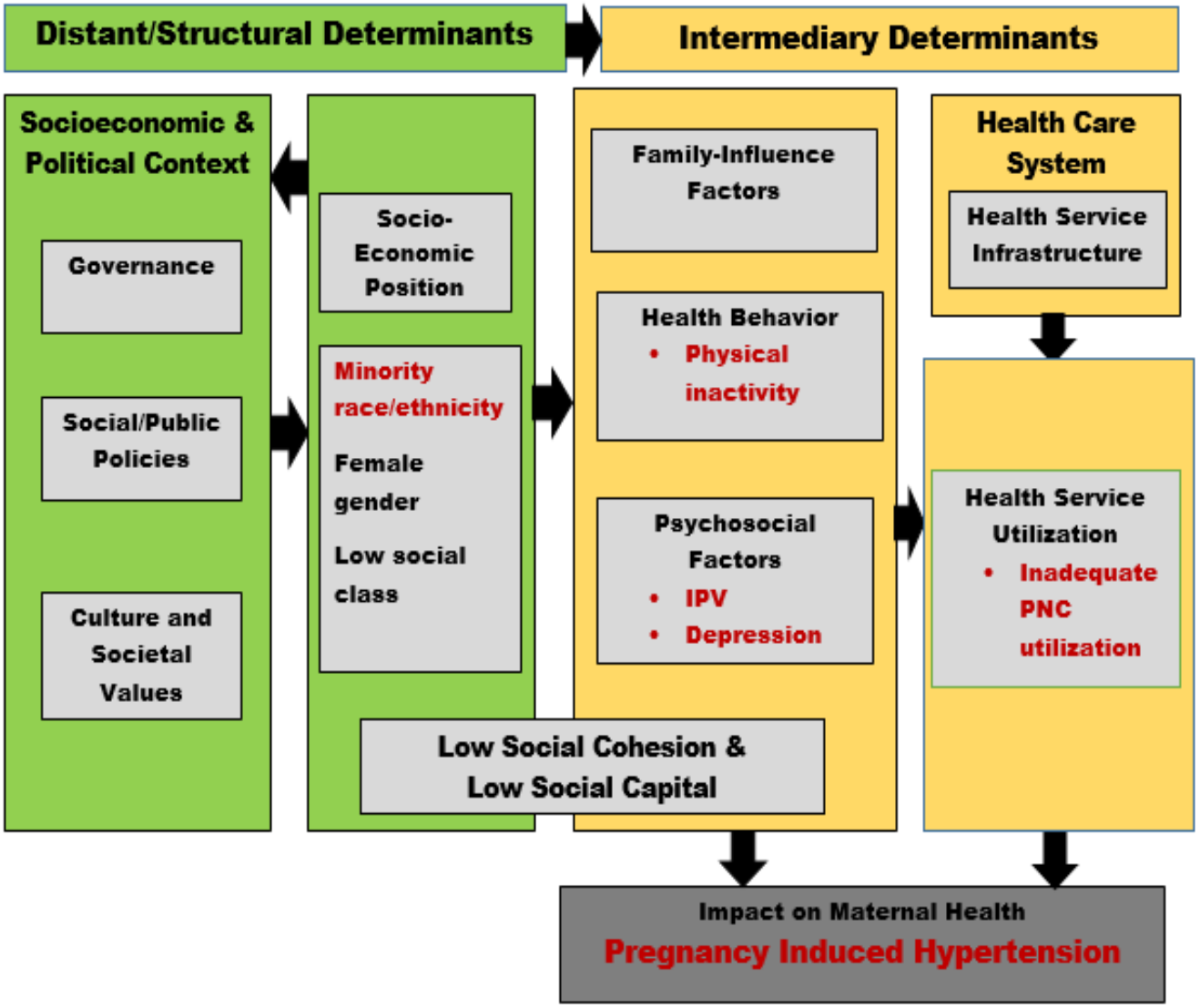

Figure 1-1. Conceptual Framework: Social Determinants of Pregnancy Induced Hypertension, Based on the Commission on Social Determinants of Maternal Health`s Framework, World Health Organization
Source: (Solar and Irwin, 2010).

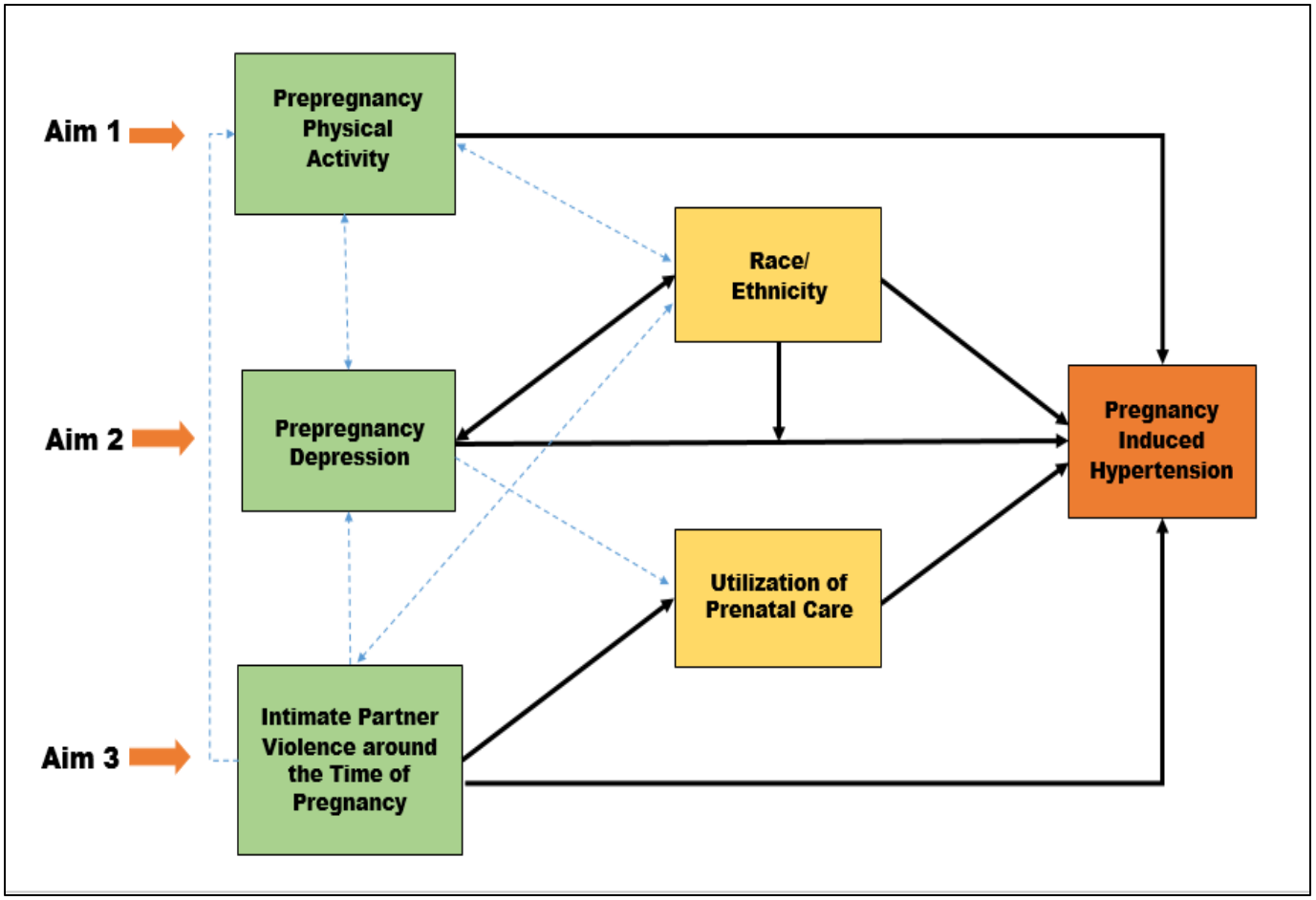

Figure 1-2. Conceptual Framework for Three Aims of the Dissertation Demonstration the Interrelationship between Psychosocial and Health Behavioral Factors and Pregnancy Induced Hypertension

Chapter 2: Overall Materials and Methods

Data Source & Study Population

Data from the National Pregnancy Risk Assessment Monitoring System (PRAMS Phase 6 & 7: Years 2009-2015) was analyzed. The national level PRAMS consists data from 47 participating states. However, this dissertation required additional birth certificate variables named 'Years since last live birth', 'Date of last live birth', 'Clinical estimate of gestational age', 'Birthweight', and 'Number of prenatal care visits' and approvals to release those additional birth certificate variables to be added to the PRAMS dataset were received from 20 states (Alaska, Colorado, Florida, Georgia, Maine, Maryland, Missouri, Nebraska, New Mexico, North Carolina, Oklahoma, Oregon, Pennsylvania, Rhode Island, Utah, Virginia, Washington, West Virginia, Wisconsin, and Wyoming). Therefore, the current study utilized PRAMS data from those 20 states (Figure 2.1).

The PRAMS is a surveillance program conducted by the Centers for Disease Control and Prevention (CDC) in collaboration with state health departments.[43] CDC established this population-based surveillance system to collect national data on maternal behaviors, attitudes and experiences before, during, and shortly after pregnancy. Participating states conduct ongoing population-based surveillance of health behaviors during pregnancy through early postpartum period by sampling 1,300-3,400 women per year with recent live births drawn from the state's birth certificate registry.[43] Data collection protocols and instruments are standardized to allow inter-state comparability. All states in the dataset maintained an overall response rate of at least 70% to minimize nonresponse bias and ensure representation of the population under study. A complex multistage sampling design was utilized and appropriate sampling, nonresponse, and non-coverage weights were applied. Women from minority groups and at-risk population were

oversampled for proper analysis. More detailed information on the methodology are available elsewhere.[43]

Inclusion and exclusion criteria

The overall study sample for these analyses included all women who delivered a singleton live birth from 20 states participating in PRAMS survey (N= 145,870). The women with multiple pregnancies (n = 8,797 (4.4%)) and hypertension prior to pregnancy (n = 25,236 (3.6%)) were excluded from the analyses. The decision to exclude multiple pregnancies and prepregnancy hypertension was based on prior studies that showed an increased risk of PIH in association with these conditions.[2,44]

Operational Definition of Outcome

Pregnancy induced hypertension (PIH), the outcome, was defined as a binary variable based on a birth certificate variable that was included in the PRAMS data. Information on eight risk factors in the current pregnancy are separately identified on the birth certificate in a checkbox format (yes, no). One of these risk factors is hypertension in this pregnancy. PIH was determined using this birth certificate variable that included either prepregnancy - (Chronic) (Hypertension diagnosed prior to the onset of this pregnancy) or Gestational - (PIH, preeclampsia, eclampsia) (Hypertension diagnosed during this pregnancy). Women who were checked as "yes" to this variables were categorized as "yes" to PIH and women who were checked as "no" to this variable were categorized as "no" to PIH. Women with hypertension diagnosed prior to this pregnancy were excluded from the analysis using a PRAMS questionnaire variable, restricting the definition of PIH for this analysis to hypertension diagnosed during this pregnancy only.

Information on risk factors in the current pregnancy that are included in the birth certificate is recommended to be collected directly from the medical record using the facility worksheet; therefore can be considered valid.[45] Information on the outcome PIH is also collected using the PRAMS survey question that asks "Did you have any of the following problems during your most recent pregnancy?" and one of the answer options is "High blood pressure, hypertension (including pregnancy-induced hypertension [PIH]), preeclampsia, or toxemia". However, we chose not to use this answer choice to define the outcome variable for the current study because it does not single out PIH. Moreover, it is self-reported and prone to error.

Operational Definition of Potential covariates

Based on previous literature,[2,3,5,6,9,12,17,22,23,25,29,30,46-50] potential covariates that may mediate, modify or confound the relationship between the exposure variables and PIH were assessed. These included socio-demographic factors, healthcare access and utilization factors, substance use/health behavioral factors, psychosocial factors, and reproductive/pregnancy history factors (Table 2-1).

Among these factors, specifically adequacy of prenatal care utilization was evaluated as potential mediators and race/ethnicity was evaluated as potential moderator based on the aims of this dissertation.

Table 2-1. Covariates Included in the Overall Analyses

Socio-Demographic Characteristics	
Maternal age	<18, 18-24; 25-29; 30-34; 35+ years
Maternal race/ethnicity	Non-Hispanic White; Non-Hispanic Black; Non-Hispanic American Indian or Alaskan Native; Non-Hispanic Asian; Non-Hispanic Hawaiian & non-White others; Hispanic
Maternal education	Less than high school; High school; Some college; Bachelor's degree or higher
Household income	<US$20,000; US$20,000-US$34,999; US$35,000 to US$49,999; US$50,000 or more
Marital status	Married; Not married
Health Care Access and Utilization	
Insurance status before pregnancy	Private insurance; Medicaid/public insurance; No insurance
Residence	Urban; Rural
Adequacy of prenatal care utilization	Inadequate; Intermediate; Adequate; Adequate plus
Health and Lifestyle Behavior	
Alcohol use before pregnancy	Yes; No
Smoking before pregnancy	Yes; No
Physical activity before pregnancy	Exercise 3+days/wk.: Yes; No
Psychosocial Factors	
Number of stressors during pregnancy	None; 1 to 2; 3 to 4; 6 or more
Prepregnancy depression	Yes; No
Intimate partner violence before/during pregnancy	Yes; No
Reproductive Factors and Pregnancy History	
Parity (Number of previous live births)	None; One; Two or more
Pregnancy intention	Intended; Unintended
Previous C-section	Yes; No
Previous termination of pregnancy	0, 1, 2+ terminations
Previous preterm birth	Yes; No
Prepregnancy body mass index (BMI) in kg/m^2	Underweight (>18.5); Normal weight (18.5-24.9); Overweight (25.0 – 29.9); Obese (≥30.0)
Prepregnancy diabetes	Yes; No
Gestational diabetes	Yes; No
Pregnancy weight gain in pounds	<11; 11 to 20; 21 to 30; 31 to 40; >40

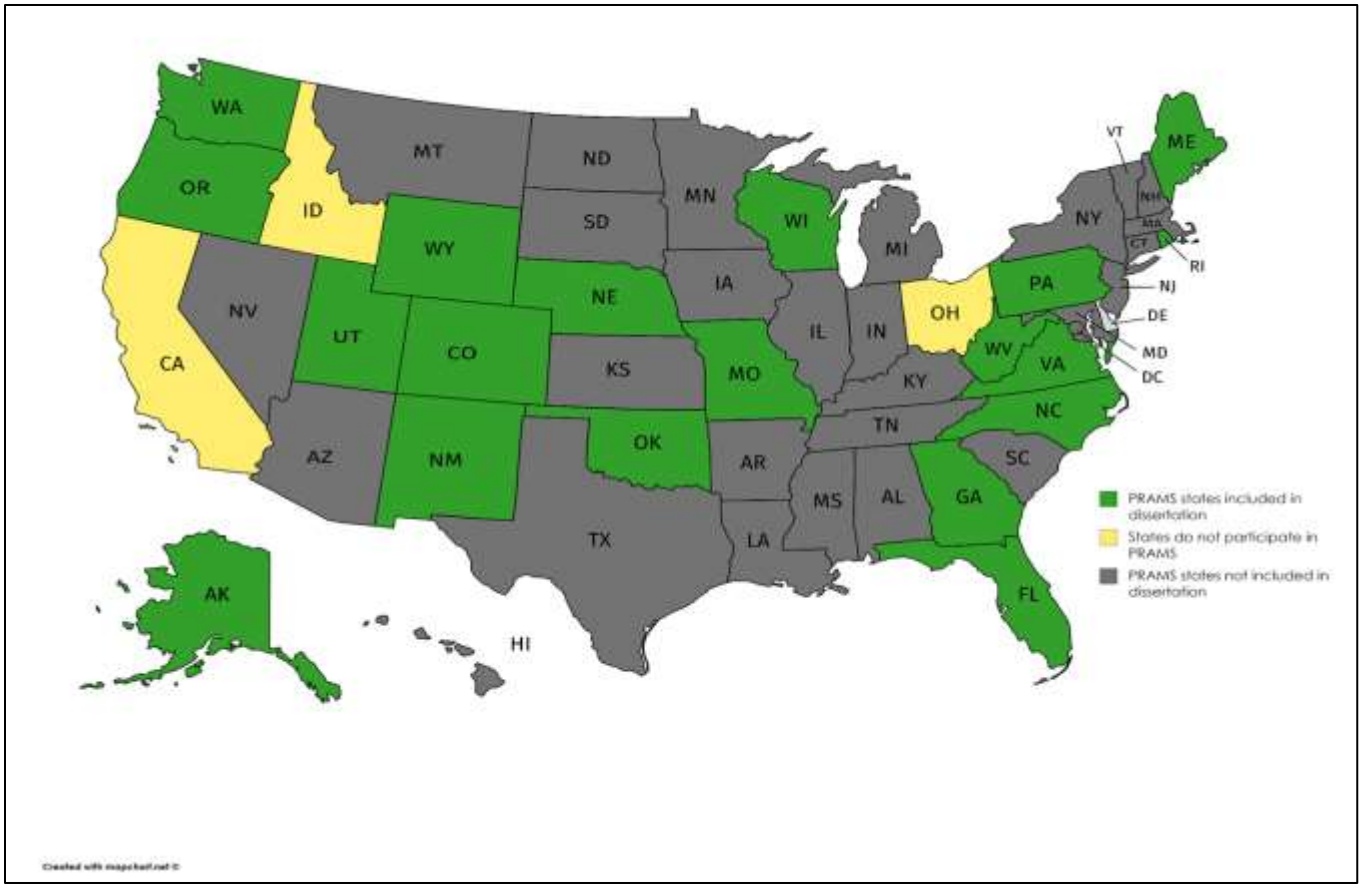

Figure 2.1. PRAMS States that were Included in the Analyses for the Dissertation

Chapter 3: Pre-pregnancy Physical Activity and the Risk of Pregnancy Induced Hypertension

Abstract

Background: Pregnancy induced hypertension (PIH) is the leading cause of maternal mortality and a major contributor to preterm birth and neonatal mortality. The incidence of PIH has increased significantly in the United States in the past two decades, complicating 5% to 10% of all pregnancies. However, the etiology of PIH remains unclear. Prepregnancy overweight/obesity, hypertension, diabetes, and cardiovascular diseases are all known risk factors for PIH. Regular physical activity is a known protective factor against obesity, hypertension, diabetes, and cardiovascular diseases and therefore, could be a potential protective factor for PIH as well. This study aims to examine the effect of pre-pregnancy physical activity on PIH.

Methods: The current study utilized Phase 6 and 7 (Year 2009-2015) of the National Pregnancy Risk Assessment Monitoring System survey data for analyses. Women with singleton births and no prior history of hypertension were included in the analysis (N=89,577). Pre-pregnancy exercise (yes; no) and PIH (gestational hypertension, preeclampsia, or eclampsia) (yes; no) were examined. Hierarchical domain-adjusted multiple logistic regression analysis was conducted, providing adjusted odds ratios with corresponding 95% confidence intervals.

Results: Almost half of the participating women reported doing exercise three days or more a week before pregnancy and 7.3% had PIH. After adjusting for sociodemographic factors domain including maternal age, race/ethnicity, marital status and education, women who did exercise three days or more a week before pregnancy were found to have a 10% lower odds of having PIH compared to women who did not exercise three days or more a week (AOR: 0.90, 95% CI: 0.79, 0.98). However, the statistical significance disappeared after further adjustment of domains of substance use/health behavioral, psychosocial, and reproductive/pregnancy history factors. In addition, older maternal age, primiparity, prepregnancy obesity/overweight, and excessive pregnancy weight gain were identified as independent risk factors for PIH in the fully adjusted model.

Conclusions: Women physically active prior to pregnancy were not found to be at reduced risk of developing PIH in the current study. Further studies using prospective cohort study design are needed to confirm the effect of pre-pregnancy physical activity on the risk of PIH.

Introduction

Pregnancy induced hypertension (PIH) refers to a clinically challenging group of pregnancy complications, including gestational hypertension, preeclampsia, eclampsia, and unclassifiable hypertension.[51] In this study, PIH is defined as the new onset of hypertensive disorder in pregnant women after 20 weeks of gestation and therefore, refers to one of the three conditions: gestational hypertension, preeclampsia, and eclampsia.[51] PIH complicates 5% to 10% of all pregnancies in the U.S.[3] and is the single leading cause of maternal mortality.[3,52] Furthermore, PIH is a major contributor to prematurity [2] and one of the most frequent causes of maternal and neonatal morbidity.[3] The incidence of PIH has increased significantly in the U.S. In the last two decades, the incidence of preeclampsia has increased by 25% and gestational hypertension by 184%.[3,12] However, the reasons for this rise are not well explored. Changes in a woman's lifestyle and characteristics altering certain behavioral factors could be responsible for the rise of PIH. For example, sedentary work environments, lack of physical activity and unhealthy diet-habits due to busy lifestyle leading to overweight and obesity in women may have contributed to the rise of gestational hypertension and preeclampsia in recent decades in the U.S.

Physical inactivity is a modifiable risk factor that plays an important role in the development of many chronic diseases and mental health disorders.[26] The prevalence of physical inactivity in the U.S. adults is about 30% when a physically inactive person is defined as a person who did not engage in physical activity or exercise during the previous 30 days other than for his/her regular job.[53] There appears to be a linear relation between physical activity and health status, such that a further increase in physical activity and fitness will lead to additional improvements in health status.[54,55] Plethora of previous literature established the evidence of protective role of regular physical activity in several chronic diseases and premature death.[27,28,56-64] For example, an article summarizing the evidence of health benefits of physical activity

in systematic reviews and meta-analyses confirmed that there is clear evidence of the effectiveness of regular physical activity in the primary and secondary prevention of several chronic diseases such as cardiovascular disease, diabetes, obesity, hypertension, cancer, depression and osteoporosis, and premature death.[26] A systematic review of the literature regarding primary prevention in women revealed that there was a graded inverse relation between physical activity and cardiovascular disease risks in women.[60]

Thus, physical inactivity is an established predictor of obesity, hypertension, cardiovascular diseases, and diabetes, and all of these conditions are known to be closely associated with PIH. For example, previous studies found a significant association between maternal obesity and increased risk of hypertensive disorder of pregnancy.[29,65] There has been a population-level significant increase in the prevalence of obesity, especially in women, in last four decades in the U.S.[66,67] that might have contributed to the rise of gestational hypertension and preeclampsia in the recent decades. Further, obesity is a risk factor for hypertension [68,69] and type 2 diabetes[70,71] and both pre-pregnancy hypertension and diabetes are known to increase the risk of PIH.[16,30,72-75] In addition, physical inactivity increases the risk of cardiovascular diseases in women [56,58,59] and cardiovascular diseases can be associated with preeclampsia, one of the PIH.[44] Similarly, regular physical activity has been shown to be associated with a decreased risk of type 2 diabetes[76-81] and pre-pregnancy diabetes has been closely linked to increased risk of PIH.[16,75]

Existing literature on association between physical activity and pregnancy outcomes mostly focused on physical activity during pregnancy. For example, a systematic review of observational and intervention studies discussing empirical evidence of prenatal activity on adverse maternal outcomes showed sedentary behaviors and/or low levels of physical activity

during pregnancy to be associated with elevated risk of gestational diabetes, pregnancy induced hypertension and high gestational weight gain.[82] Several prior epidemiologic studies observed physical activity during early pregnancy to have a protective effect on preeclampsia.[83,84] Only two case control studies, to the knowledge of the author, looking into the association between pre-pregnancy physical activity and preeclampsia suggested a decreased risk of preeclampsia for women who participated in any recreational physical activity during the year prior to pregnancy.[85,86] However, these two studies included only recreational physical activity as exposure, giving a rather narrow definition of physical activity and analyzed preeclampsia as the outcome, leaving behind gestational hypertension, the most common form of PIH. Further, several prospective cohort studies found no significant association between pre-pregnancy physical activity and preeclampsia.[87-89]

Prepregnancy overweight/obesity, hypertension, diabetes, and cardiovascular diseases are all well-established and modifiable risk factors of PIH.[29,30,44,65,72-75] Regular physical activity is a known protective factor against obesity, hypertension, diabetes, and cardiovascular diseases and therefore, could be a potential protective factor for PIH as well. Studies are needed to establish the association between physical activity prior to pregnancy and PIH. Moreover, these studies need to include all forms of PIH, including gestational hypertension, to capture the true association between pre-pregnancy physical activity and PIH. The current study analyzes pre-pregnancy physical activity defined by any forms of exercising three or more days a week during 12 months prior to pregnancy. Further, the current study includes gestational hypertension, preeclampsia, and eclampsia providing a more inclusive definition of PIH. The study aims to examine the effect of physical activity before pregnancy on the risk of pregnancy induced

hypertension and we hypothesize than being physically active before pregnancy is inversely associated with the risk of PIH.

Materials and Methods

This was a cross-sectional study using data from the National Pregnancy Risk Assessment Monitoring System (PRAMS Phase 6 and 7: Years 2009-2015) survey. The national level PRAMS consists data from 47 participating states. However, the current study required additional birth certificate variables named 'Years since last live birth', 'Date of last live birth', Clinical estimate of gestational age', 'Birthweight', and 'Number of prenatal care visits' and approvals to release those additional birth certificate variables to be added to the PRAMS dataset were received from 20 states (Alaska, Colorado, Florida, Georgia, Maine, Maryland, Missouri, Nebraska, New Mexico, North Carolina, Oklahoma, Oregon, Pennsylvania, Rhode Island, Utah, Virginia, Washington, West Virginia, Wisconsin, and Wyoming). Therefore, the current study utilized PRAMS data from those 20 states.

The PRAMS is a surveillance program conducted by the Centers for Disease Control and Prevention (CDC) in collaboration with state health departments.[50(43)] Between 1,300 and 3,400 women, who have had a recent live birth, are sampled each year from the respective state's birth certificate file. The PRAMS collects national data on maternal behaviors, attitudes and experiences before, during, and shortly after pregnancy using a standardized data collection methodology.[43] Mother's responses are then linked to the corresponding birth certificate data. A complex multistage sampling design is utilized and appropriate sampling, nonresponse, and non-coverage weights are applied. Women from minority groups and at-risk population are oversampled for proper analysis. More detailed information on the methodology are available elsewhere.[43] The PRAMS study protocol for this study was approved by participating states and

the Centers for Disease Control and Prevention Institutional Review Board. Further, the Virginia Commonwealth University Institution Review Board deemed this study exempt.

Study Sample, Inclusion and Exclusion Criteria

Mothers from 20 states participating in PRAMS survey (N= 145,870) who delivered a singleton live birth in the years of 2009 to 2015 were initially included in this study. The study then excluded women who had multiple pregnancies (twin, triplets, etc.) (4.4%),[44] hypertension prior to pregnancy (3.6%),[30,72,73] or did not give valid responses to outcome and/or exposure variable (30.6%) leaving 89,577 women for current analysis (Figure 3-1).

Operational Definition of Outcome

Pregnancy induced hypertension (PIH), the outcome, was defined as a binary variable based on a birth certificate variable that was included in the PRAMS data. Information on six risk factors in the current pregnancy are separately identified on the birth certificate in a checkbox format (yes, no). One of these six risk factors is hypertension during this pregnancy. PIH was determined using this birth certificate variable that included either prepregnancy - (Chronic) (Hypertension diagnosed prior to the onset of this pregnancy) or Gestational - (PIH, preeclampsia, eclampsia) (Hypertension diagnosed during this pregnancy). Women who were checked as "yes" to this variables were categorized as "yes" to PIH and women who were checked as "no" to this variable were categorized as "no" to PIH. Women with hypertension diagnosed prior to this pregnancy were excluded from the analysis using a PRAMS questionnaire variable, restricting the definition of PIH for this analysis to hypertension diagnosed during this pregnancy only.

Operational definition of exposure

Exposure variable, physical activity before pregnancy, was based on the PRAMS survey question that asked women information regarding their pre-conception readiness, "During 12 months *before* you got pregnant with your new baby, did you do any of the following?" The only answer option related to physical activity was "I was exercising 3 or more days of the week" (yes, no). This option was used to create a binary variable indicating pre-pregnancy exercise (0 = no, 1 = yes).

Operational definition of potential Covariates

A variety of covariates identified in the literature[2,3,26,44,51,52,74,76,82-84,86] were assessed as potential confounders or effect modifiers in the association between physical activity before pregnancy and PIH (Figure 3-2). These included sociodemographic factors: maternal age (<18, 18-24, 25-29, 30-34, 35+ years), maternal race (non-Hispanic white, non-Hispanic black, non-Hispanic other, Hispanic), maternal education (less than high school, high school, some college, bachelor's degree or higher), marital status (married, not married), and household income (<US$20,000; US$20,000-US$34,999; US$35,000- US$49,999; US$50,000+); health care access and utilization factors: insurance status before pregnancy (private insurance, Medicaid/public insurance, no insurance), adequacy of prenatal care utilization (Kotelchuck index: inadequate, intermediate, adequate, adequate plus) and residence (urban, rural); substance use/health behavioral factors: alcohol use in last 2 years (yes, no), smoking in last 2 years (yes, no); psychosocial factor: prepregnancy depression (yes, no), pre-pregnancy intimate partner violence (yes, no) and number of stressors during 12 months prior to childbirth (none, 1 or 2, 3-5, 6+); and reproductive factors and pregnancy history: parity (number of previous live births) (0, 1, 2+), previous preterm birth (yes, no), previous C-section (yes, no), prepregnancy diabetes (yes, no), prepregnancy body mass index (BMI) (underweight: >18.5, normal weight: 18.5-24.9,

overweight: 25.0 – 29.9, obese: ≥30.0 kg/m^2), pregnancy weight gain (<11 lbs., 11 to 20 lbs., 21 to 30 lbs., 31 to 40 lbs., >40 lbs.), and gestational diabetes (yes, no).

Statistical Analysis

All analyses were conducted in SAS 9.4 with adjustments for the complex sample design of the PRAMS to provide population estimates that represent the states that participated in the Phase 6 and 7 PRAMS survey. Descriptive statistics including frequencies and percentages were generated to assess the distribution of characteristics among participants, overall and by pre-pregnancy exercise and PIH. The sub-populations were compared through chi-squared tests to determine if statistically significant differences existed between the study groups by pre-pregnancy exercise and by PIH. Bivariate regressions analysis provided crude odds ratios and 95% confidence intervals determining the factors associated with PIH. Multicollinearity was tested for the covariates using variance inflation factor (VIF).[90]

Thereafter, a domain-adjusted multiple logistic regression analysis was performed.[91] Four separate multiple logistic regression models were evaluated by stepwise addition of one domain of confounders at a time to evaluate the differences in effect-size estimates of the association between pre-pregnancy exercise and PIH after adjusting for each additional domain. The domains included sociodemographic factors, substance use/health behavioral factors, psychosocial factors, and reproductive/pregnancy history factors. Model A was adjusted for sociodemographic factors; model B was adjusted for sociodemographic plus substance use/health behavioral factors; model C was adjusted for sociodemographic plus substance use/health behavioral plus psychosocial factors; and model D was adjusted for sociodemographic plus substance use/health behavioral plus psychosocial plus reproductive/pregnancy history factors. Hierarchical backward elimination was conducted to identify a parsimonious model for each of these four separate multiple logistic regression analyses.[91] Initial models contained exposure, outcome and all

covariates for that domain/s. First, effect-modification by maternal race/ethnicity, maternal education, parity, pre-pregnancy diabetes, and pre-pregnancy BMI were assessed using the likelihood ratio test, as these variables were identified as possible effect modifiers in the prior literature review.[2,26,44,52,54,74,82,86] Following assessment for effect modifications, confounding was assessed using the 10% change-in-estimate method for each model.[91,92] The final multiple logistic regression models provided adjusted odds ratios and their 95% confidence intervals determining the associations between pre-pregnancy exercise and PIH for four different models. The overall adjusted level of significance for all analyses was set to a p-value of 0.05.

Results

Among the study population, 7.3% women were diagnosed with PIH during their most recent pregnancy and 47.9% of women reported doing exercise three or more days of the week during 12 months before their pregnancy. Table 3-1 presents the weighted percentages of the characteristics of the study population, overall and by pre-pregnancy exercise. Majority of the study population were age 25 years or older (71.3%), non-Hispanic White (66.3%), married (63.9%), had a high school or greater education level (86.8%) and reported a household income of $20,000 or more per year (70.6%). For factors associated with healthcare access, majority of the women had private health insurance (61.5%) and reported living in an urban area (65.3%). In regards to reproductive and pregnancy history, more than half of the women had at least one previous live birth (59.7), were normal or underweight before pregnancy (51.7%), and gained more than 20 lbs. during their most recent pregnancy (71.3%). Further, over ninety percent of the women reported no previous preterm birth, prepregnancy diabetes, or gestational diabetes during their recent pregnancy. Lastly, most women reported not smoking in the previous two years

(75.1%), but majority reported drinking alcohol in the same period (64.5%) and having at least one stressor in life during their most recent pregnancy (70.7%).

The majority of the women who exercised 3 or more days a week before pregnancy were under the age of 35 years (85.0%), non-Hispanic White (71.8%), married (70.8%), had more than a high school level education (70.6%), and had an annual income more than $35,000 (54.3%) (Table 3-1). Further, among those who exercised, 68.8% had private insurance, 55.6% had one or no stressor in life during pregnancy, 74.1% had one or no previous live birth, and 53.6% were normal or underweight before pregnancy. Percentage of women who smoked before pregnancy, reported IPV and depression before pregnancy, and had gestational diabetes during pregnancy were higher among women who did not exercise compared to those who exercised before pregnancy. Rao-Scott Chi-square tests indicated a statistically significant association between pre-pregnancy exercise and all of the covariates except residence and pre-pregnancy diabetes (Table 3-1).

The prevalence of PIH was significantly higher among women age 35 years or more, who were unmarried, obese or overweight, had lower education, inadequate or adequate plus prenatal care utilization, and history of smoking or drinking alcohol (Table 3-1). Further, women who were nulliparous and had history of preterm births, prepregnancy diabetes, or gestational diabetes had a significantly higher prevalence of PIH.

Table 3-2 shows the results of bivariate and domain-adjusted multiple logistic regression model analyses assessing the unadjusted and adjusted association between pre-pregnancy exercise and PIH. Bivariate logistic regression analyses showed statistically significant associations between PIH and maternal age, race/ethnicity, maternal education, marital status, prenatal care utilization, smoking and drinking alcohol two years before pregnancy,

prepregnancy depression, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, and pregnancy weight gain. The tests for multicollinearity using VIF showed household income to be highly correlated to maternal age, education, marital status, and insurance status, and therefore, household income was excluded from further analyses. None of the covariates was identified as effect-modifier. The covariates that were identified as potential confounders using 10% change-in-estimate method included maternal age, race/ethnicity, education and marital status for the sociodemographic factors domain; smoking and alcohol use for the substance use/health behavioral factors domain; prepregnancy depression for the psychosocial factor domain; and parity, prepregnancy BMI, and pregnancy weight gain for the reproductive/pregnancy history factors domain.

In the unadjusted analysis, women who exercised 3 or more days a week during 12 months before pregnancy had 16% less odds of developing PIH compared to women who did not exercise (crude odds ratio (COR): 0.84, 95% CI: 0.76, 0.94) (Table 3-2). The strength of this association weakened but remained statistically significant after adjusting for the sociodemographic factors domain in the adjusted model A (adjusted odds ratio (AOR): 0.89, 95% CI: 0.77, 0.97). However, after additionally adjusting for the domain of substance use/health behavioral factors in Model B, the association lost its statistical significance. Additional adjustments with psychosocial factor domain in Model C and reproductive/pregnancy history factors domain in Model D showed similar statistical insignificance. Maternal age, race/ethnicity, parity, prepregnancy BMI, and pregnancy weight gain were found to be statistically significantly associated with PIH in the fully adjusted final model.

Discussion

The current study found no statistically significant association between pre-pregnancy

physical activity and PIH in the fully adjusted analysis. This finding is consistent with prior studies that demonstrated no significant association between pre-pregnancy physical activity and preeclampsia.[87-89] However, in the unadjusted analysis and in the analysis adjusted for maternal age, race/ethnicity, education, and marital status, a statistically significant inverse association between physical activity before pregnancy and risk of PIH was observed in the current study. A number of research have demonstrated that being physically active is integral for individuals to preserve physical and psychological health.[26,54,55,57] A few prior studies have also shown an inverse relationship between physical activity and preeclampsia;[82-86] however, these studies examined the effect of physical activity during pregnancy only, not before pregnancy, and did not include gestational hypertension as outcome. The current study found that participating women who exercised three or more days a week during 12 months before pregnancy were significantly less likely to have PIH, including gestational hypertension, preeclampsia or eclampsia compared to women who did not exercise before pregnancy in the analysis adjusted for demographic characteristics.

The inverse association between physical activity before pregnancy and risk of PIH can be explained by the fact that sedentary behaviors and/or low levels of physical activity before pregnancy increase the risk of obesity/overweight, hypertension, diabetes and cardiovascular diseases, and all these conditions are known risk factors of PIH. This explanation is corroborated with previous research investigating the associations between physical activity and chronic diseases and between chronic diseases and PIH.[27-30,44,56,58-65,72-75]

Several biological mechanisms may be responsible for the reduction in the risk of obesity/overweight, hypertension, diabetes and cardiovascular diseases associated with routine physical activity. For example, routine physical activity has been shown to reduce the risk of

obesity and overweight by improving body composition and reducing fat stores through improved endothelial function, reduced abdominal adiposity and improved weight control;[76,77,93-97] and higher prepregnancy BMI is known to increases the risk of PIH either directly [29,65,98] or indirectly by increasing the risk of hypertension [68,69] and/or diabetes [70,71] prior to pregnancy. Furthermore, routine physical activity reduces the risk of hypertension by lowering the blood pressure,[62,99-101] improving the coronary blood flow,[102] improving the autonomic tone,[103,104] and enhancing the endothelial function;[105-108] and reduced risk of pre-pregnancy hypertension may reduce the risk of PIH, as PIH is a hypertensive disorder and pre-pregnancy hypertension is known to increase the risk of PIH.[30,72-74] Moreover, both aerobic and resistance types of exercise have been shown to be associated with a decreased risk of type 2 diabetes by improving glucose homeostasis and insulin sensitivity; [76-81,93,109-111] and pre-pregnancy type 2 diabetes is known to increases the risk of PIH.[16,75]

In addition, routine physical activity can reduce the risk of cardiovascular diseases by enhancing lipid lipoprotein profiles,[76,93,112-114] by decreasing blood coagulation,[115,116] and by augmenting cardiac function;[117,118] and cardiovascular diseases may be associated with PIH through similar risk factors and pathophysiology, such as involvement of endothelial dysfunction, platelet dysfunction and sympathetic over-activity.[44]

Of note, the inverse association between physical activity and risk of PIH lost its statistical significance in the current study after adjusting for additional domains of substance use/health behavioral factors, psychosocial factors, and pregnancy history/reproductive factors. The reason for that could be the probability that some of the factors in these domains that were adjusted for actually were on the causal pathway from pre-pregnancy physical activity to PIH. For example, pre-pregnancy exercise can reduce maternal pre-pregnancy BMI [93-97] and reduced

pre-pregnancy BMI is known to be associated with reduced risk of PIH.[29,65] Similarly, women who are physically active before pregnancy tend to remain physically active during pregnancy as well and they usually gain appropriate weight during pregnancy; and thereby may reduce their risk of PIH as excessive weight gain during pregnancy is a known risk factor for PIH.[98] In addition, routine physical activity is also associated with improved psychological well-being through reduced stress, anxiety and depression;[38,93,119] and reduced depression can lead to reduced risk of PIH by lowering the likelihood of chronic diseases such as diabetes, hypertension and obesity.[44,119] Further, hypertension could be one of the major explanatory factors on the causal pathway in the inverse relationship between pre-pregnancy physical activity and risk of PIH; but women with pre-pregnancy hypertension had to be excluded from the current analyses to define PIH validly and inclusively, and that might have caused underestimation of the association leading to insignificant findings.

This study has several limitations. It is limited by the cross-sectional nature of the PRAMS data making it susceptible to residual confounding and limiting the determination of causality. However, due to the temporal sequence between pre-pregnancy physical activity and PIH, temporality can be assumed. The study is further limited by lack of information on several factors that are strongly associated with PIH, such as history of chronic renal disease, antihypertensive treatment, history of cardiovascular diseases and history of preeclampsia or gestational hypertension in a previous pregnancy.[44] Inability to assess and adjust for these factors might have introduced bias in the current study causing overestimation or underestimation of the effects. For example, women with cardiovascular diseases before pregnancy might have been engaged in less physical activity, potentially increasing their risk of developing PIH. Inability to adjust for history of cardiovascular diseases prior to pregnancy might have caused

underestimation of the protective effect of pre-pregnancy physical activity on risk of PIH, leading to finding of non-significant association in the current study. Further, previous studies demonstrated an association between exercise during pregnancy and preeclampsia,[82,84] but information on physical activity during pregnancy was not available in the dataset and therefore could not be assessed. In addition, the sample for the current study comes from 20 states, instead of all 47 states that participates in national level PRAMS survey. This might have reduced the generalizability of the inference of this study to the overall U.S. women. However, these 20 states are scattered all over the U.S. representing all four Northeast, Midwest, South, and West regions, and therefore can be considered as representative of general U.S. population. Lastly, the exposure measure, pre-pregnancy exercise, was self-reported and therefore could be susceptible to desirability bias, and also without intensity measures potentially causing dilution of effects, leading to underestimation of association.

Despite its limitation, the current study has a number of notable strengths. To the authors' knowledge, this is the first study to investigate the effect of physical activity before pregnancy on the risk of PIH, including gestational hypertension, preeclampsia and eclampsia. The major strength of the study is that, in addition to using the PRAMS, a robust population-based dataset with a large sample size, the current study utilized data on several additional birth certificate variables, information for which were collected directly from the medical record by a health professional using the facility worksheet; therefore can be considered valid.[45] Further, The current analysis was performed using a nationally representative sample of women which allows for inference to the general U.S. women population. The outcome measure, pregnancy induced hypertension, was based on a birth certificate variable, therefore can be considered valid.[83]

Conclusion

The current study suggests that women physically active prior to pregnancy are not at reduced risk of developing PIH compared to women who are sedentary. However, this finding should be viewed considering the limitations of this study mentioned earlier. Future studies are needed to confirm the effect of pre-pregnancy physical activity on the occurrence of PIH using prospective cohort study design. Research is also recommended to look into the possible mediating roles of pre-pregnancy BMI, prepregnancy HTN and pre-pregnancy diabetes on the causal pathway from physical activity before pregnancy to development of PIH utilizing longitudinal dataset. Future research is further recommended to look into the combined effect of prepregnancy and prenatal increased physical activity on the risk of PIH.

Table 3-1. Characteristics of the Study Population Overall, by Pre-pregnancy Physical Activity and by Pregnancy Induced Hypertension; PRAMS 2009-2015

Characteristics	Total (N=89,577)	Pre-pregnancy Exercise (N=42,953; 47.9%	P-value (Rao-Scott Chi^2 Test)	PIH (N=6,482; 7.3%)	P-value (Rao-Scott Chi^2 Test)
	%	*%*		**Prevalence**	
Socio-Demographic Factors					
Maternal Age			<.0001		0.0636
<18 years.	6.6	5.8		6.1	
18 -24 years	22.1	18.7		4.8	
25-29 years	30.9	31.2		5.2	
30- 34 years	26.5	29.3		5.5	
35+ years	13.9	15.0		5.7	
Race/Ethnicity			<.0001		<.0001
Non-Hispanic White	66.3	71.8		5.5	
Non-Hispanic Black	11.2	7.9		7.4	
Non-Hispanic Other	8.6	7.9		4.6	
Hispanic	13.9	12.4		3.9	
Maternal Education			<.0001		0.0034
Less than high School	13.2	10.1		5.1	
High School	24.1	19.3		5.4	
Some College	29.2	28.5		5.9	
Bachelor's degree or higher	33.5	42.1		4.9	
Marital Status: Not Married	36.1	29.2	<.0001	5.7	0.0108
Married	63.9	70.8		5.1	
Household Income			<.0001		0.3162
Less than $20,000	35.4	27.5		4.9	
$20,000 to 34,999	19.0	18.2		6.0	
$35,000 to 49,999	12.7	13.6		4.8	
$50,000 or more	32.9	40.7		5.3	
Healthcare Access and Utilization Factors					
Insurance before Pregnancy			<.0001		0.6781
Private insurance	61.5	68.8		5.4	
Medicaid/Public insurance	17.4	14.3		5.4	
No insurance	21.1	16.9		5.6	
Adequacy of Prenatal Care Utilization			<.0001		<.0001
Inadequate	12.0	10.5		4.5	
Intermediate	12.5	12.6		3.4	
Adequate	48.2	49.7		4.2	

Adequate plus	27.3	27.2		8.6	
Residence: Rural	34.7	34.4	0.4125	5.4	0.9001
Urban	65.3	65.6		94.6	
Substance Use/Health Behavioral Factors					
Smoked before Pregnancy: Yes	24.9	20.5	<.0001	5.9	0.0046
No	75.1	79.5		5.1	
Alcohol Use before Pregnancy			<.0001		0.0067
Yes	64.5	67.4		5.6	
No	35.5	32.6		4.9	
Psychosocial Factors					
Prepregnancy Depression: Yes	9.8	8.5	<.0001	7.2	0.0120
No	90.2	91.5		5.2	
IPV before pregnancy: Yes	2.6	2.1	<.0001	6.3	0.1020
No	97.4	97.9		5.3	
Number of Stressors during			<.0001		0.3392
pregnancy: None	29.4	30.4		5.2	
1 to 2	24.2	25.2		5.1	
3 to 5	17.4	17.6		5.4	
6+	29.1	26.8		5.6	
Reproductive Factors and Pregnancy History					
Previous Live Births: None	40.3	43.9	<.0001	7.1	<.0001
One	32.3	30.2		4.1	
Two or more	27.4	25.9		4.2	
Previous Preterm Birth: Yes	3.3	3.0	0.0007	7.8	<.0001
No	96.7	97.0		5.2	
Previous C-Section: Yes	11.0	10.1	<.0001	5.8	0.1483
No	89.0	89.9		5.3	
Prepregnancy BMI (kg/m^2)			<.0001		<.0001
Underweight (<18.5)	3.6	2.7		3.1	
Normal BMI (18.5 - 24.9)	48.1	50.9		3.4	
Overweight (25.0 -29.9)	25.0	25.7		5.4	
Obese (>=30.0)	23.3	20.7		9.2	
Prepregnancy Diabetes: Yes	1.2	1.1	0.0806	12.8	<.0001
No	98.8	98.9		5.2	
Gestational Diabetes: Yes	5.1	4.7	0.0005	10.6	<.0001
No	94.9	95.3		5.0	
Pregnancy Weight Gain			<.0001		<.0001
Less than 11 lbs.	5.9	4.3		5.6	
11 to 20 lbs.	15.4	13.2		5.0	
21 to 30 lbs.	28.8	29.1		4.2	
31 to 40 lbs.	27.4	29.0		4.9	
More than 40 lbs.	22.5	24.4		7.6	

Abbreviations: PIH, pregnancy induced hypertension; IPV, intimate partner violence; BMI, Body Mass Index

Table 3-2. Unadjusted and Adjusted Odds of Pregnancy Induced Hypertension by Pre-pregnancy Physical Activity; PRAMS 2009-2015

	Crude OR (95% CI)	**Adjusted OR[a] (95% CI)**	**Adjusted OR[b] (95% CI)**	**Adjusted OR[c] (95% CI)**	**Adjusted OR[d] (95% CI)**
Pre-pregnancy Exercise: Yes	**0.84 (0.76, 0.94)**	**0.89 (0.77, 0.97)**	1.01 (0.93, 1.11)	1.03 (0.93, 1.13)	0.93 (0.89, 1.01)
No	1.00	1.00	1.00	1.00	1.00
Socio-Demographic Factors					
Maternal Age					
<18 years.	1.19 (0.98, 1.44)	1.14 (0.93, 1.40)	1.18 (0.96, 1.46)	1.19 (0.97, 1.47)	0.97 (0.75, 1.26)
18 -24 years	0.92 (0.81, 1.05)	**0.85 (0.75, 0.98)**	**0.86 (0.75, 0.99)**	**0.86 (0.75, 0.99)**	**0.79 (0.67, 0.93)**
30- 34 years	1.05 (0.94, 1.18)	1.10 (0.97, 1.24)	1.09 (0.96, 1.23)	1.09 (0.96, 1.23)	**1.17 (1.02, 1.35)**
35+ years	**1.10 (1.01, 1.24)**	**1.14 (1.03, 1.30)**	**1.13 (1.01, 1.23)**	**1.12 (1.02, 1.30)**	**1.24 (1.05, 1.46)**
25-29 years	1.00	1.00	1.00	1.00	1.00
Race/Ethnicity					
Non-Hispanic Blacks	**1.27 (1.02, 1.34)**	1.10 (0.93, 1.27)	1.15 (0.99, 1.33)	1.15 (0.99, 1.34)	1.11 (0.93, 1.32)
Non-Hispanic Others	**0.83 (0.72, 0.97)**	**0.83 (0.72, 0.97)**	**0.84 (0.73, 0.98)**	**0.84 (0.72, 0.98)**	0.89 (0.75, 1.05)
Hispanic	**0.71 (0.62, 0.81)**	**0.69 (0.59, 0.79)**	**0.72 (0.62, 0.83)**	**0.73 (0.63, 0.84)**	**0.77 (0.66, 0.91)**
Non-Hispanic White	1.00	1.00	1.00	1.00	1.00
Maternal Education					
Less than high school	1.05 (0.90, 1.22)	1.13 (0.95, 1.35)	1.13 (0.98, 1.35)	1.12 (0.93, 1.34)	1.22 (0.98, 1.52)
High school	1.12 (0.99, 1.26)	**1.17 (1.02, 1.35)**	**1.16 (1.01, 1.35)**	1.16 (1.00, 1.24)	1.17 (0.98, 1.40)
Some college	**1.23 (1.10, 1.38)**	**1.27 (1.13,1.43)**	**1.27 (1.12, 1.43)**	**1.26 (1.12, 1.42)**	1.20 (1.04, 1.38)
Bachelor's degree or higher	1.00	1.00	1.00	1.00	1.00
Marital Status					
Not Married	**1.13 (1.03, 1.24)**	**1.12 (1.01, 1.26)**	1.10 (0.98, 1.24)	1.09 (0.97, 1.23)	1.00 (0.87, 1.14)
Married	1.00	1.00	1.00	1.00	1.00
Substance Use/Health Behavioral Factors					
Smoked before Pregnancy: Yes	**1.16 (1.05, 1.28)**	-	1.06 (0.94, 1.20)	1.05 (0.93, 1.19)	0.92 (0.80, 1.06)
No	1.00	-	1.00	1.00	1.00
Alcohol Use before Pregnancy: Yes	**1.14**	-	1.09	1.09	0.99

	(1.04, 1.25)		(0.99, 1.21)	(0.99, 1.21)	(0.88, 1.12)
No	1.00	-	1.00	1.00	1.00
Psychosocial Factors					
Prepregnancy Depression: Yes	**1.36 (1.22, 1.51)**	-	-	**1.10 (1.01, 1.26)**	1.00 (0.84, 1.18)
No	1.00	-	-	1.00	1.00
Reproductive Factors and Pregnancy History					
Previous Live Births: None	**1.73 (1.54, 1.93)**	-	-	-	**2.04 (1.76, 2.37)**
One	0.96 (0.84, 1.09)	-	-	-	1.05 (0.90, 1.23)
Two or more	1.00	-	-	-	1.00
Prepregnancy BMI					
Obese (>=30.0)	**2.83 (2.52, 3.18)**	-	-	-	**3.45 (3.01, 3.94)**
Overweight (25.0 -29.9)	**1.60 (1.40, 1.82)**	-	-	-	**1.74 (1.52, 2.00)**
Underweight (<18.5)	0.88 (0.63, 1.25)	-	-	-	0.86 (0.59, 1.25)
Normal BMI (18.5 - 24.9)	1.00	-	-	-	1.00
Pregnancy Weight Gain					
More than 40 lbs.	**1.90 (1.67, 2.16)**	-	-	-	**1.90 (1.65, 2.20)**
31 to 40 lbs.	**1.19 (1.04, 1.36)**	-	-	-	**1.29 (1.11, 1.49)**
11 to 20 lbs.	**1.22 (1.04, 1.42)**	-	-	-	1.01 (0.85, 1.21)
Less than 11 lbs.	**1.37 (1.11, 1.69)**	-	-	-	0.88 (0.69, 1.12)
21 to 30 lbs.	1.00	-	-	-	1.00

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Model A: Adjusted for sociodemographic factors (maternal age, race/ethnicity, education & marital status)

[b] Model B: Adjusted for sociodemographic + substance use/health behavioral (smoking and alcohol use) factors

[c] Model C: Adjusted for sociodemographic + substance use/health behavioral + psychosocial (pre-pregnancy depression) factors

[d] Model D: Adjusted for sociodemographic + substance use/health behavioral + psychosocial + reproductive/pregnancy history (parity, pre-pregnancy BMI, & pregnancy weight gain) factors

Bold: Level of significance P <0.05

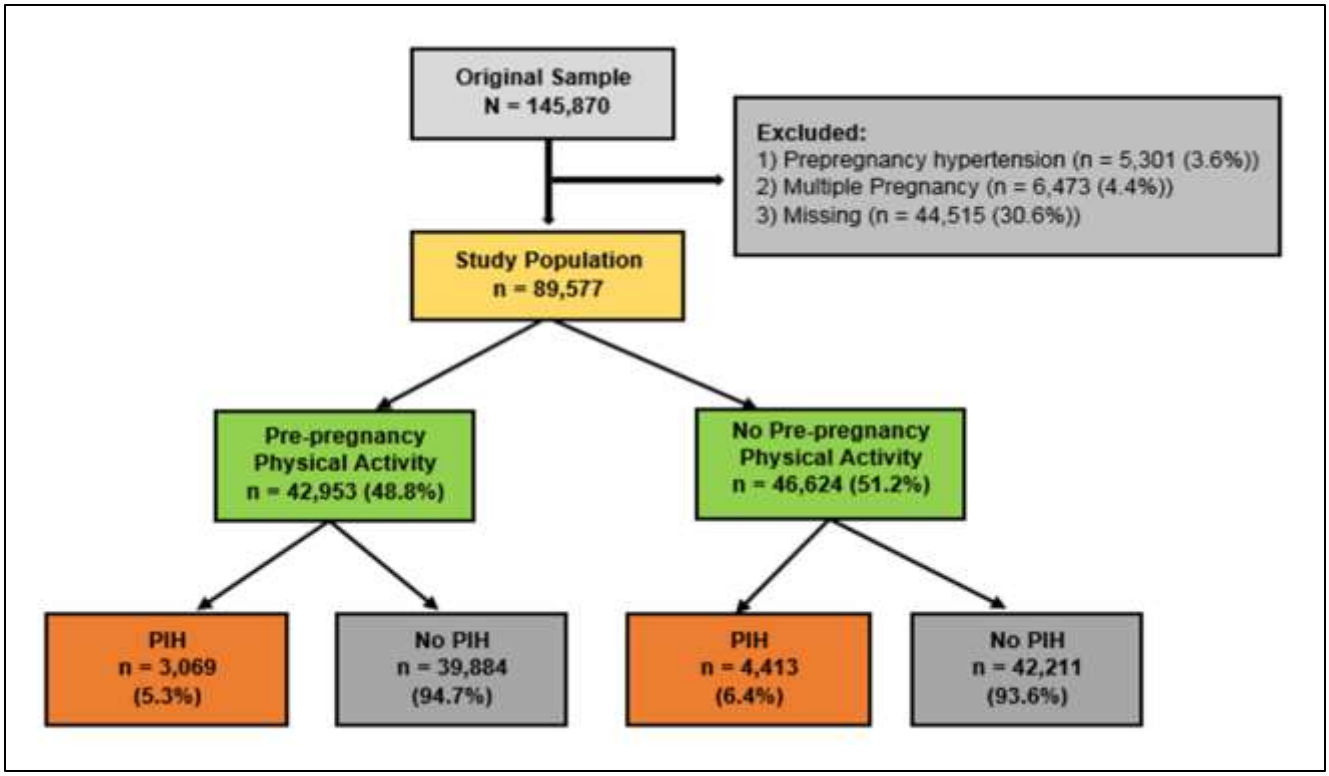

Figure 3-1. A flow diagram displaying distribution of study population in relation to exclusion criteria, pre-pregnancy physical activity, and pregnancy induced hypertension.

PIH = Pregnancy Induced Hypertension
* P value =0.0220

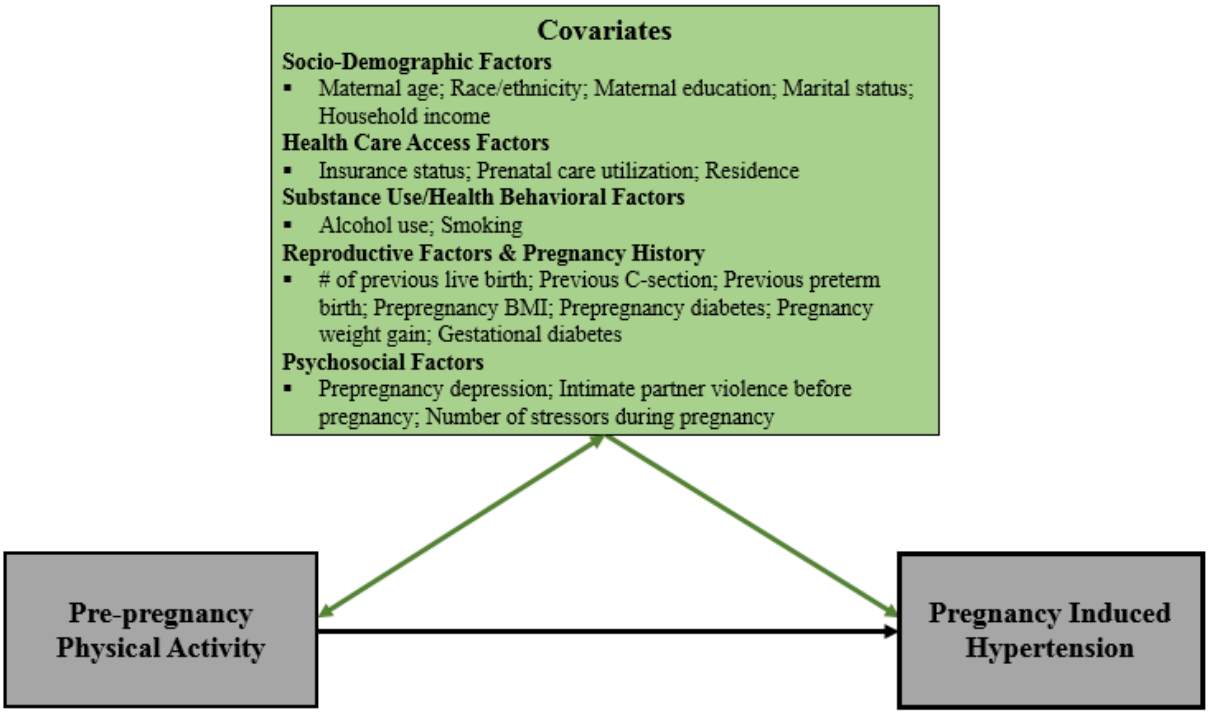

Figure 3-2. A conceptual model of the association between pre-pregnancy physical activity and pregnancy induced hypertension

Chapter 4: Association between Prepregnancy Depression and Pregnancy Induced Hypertension: Role of Race /Ethnicity

Abstract

Background: Pregnancy induced hypertension (PIH) constitutes one of the most frequent causes of maternal and neonatal morbidity, complicating up to 10% of all pregnancies in the U.S. In the last two decades, there has been a significant rise in PIH in the U.S., although the etiology remains unclear. Depression is an independent risk factor for hypertension and cardiovascular diseases, and might be a potential risk factor for PIH. Further, this association might be confounded or moderated by race/ethnicity. This study examines the association between prepregnancy depression and PIH and the role of maternal race-ethnicity in this association.

Methods: The National Pregnancy Risk Assessment Monitoring System (Phase 6 and 7: 2009–2015) survey was analyzed for the current study. Women with singleton births and no prior history of hypertension were included in the analysis (N=89,986). Prepregnancy depression (yes; no), race/ethnicity (non-Hispanic White; non-Hispanic Blacks; non-Hispanic American Indian or Alaskan Native; non-Hispanic Asian, non-Hispanic Hawaiian or non-White others; Hispanic), and PIH (gestational hypertension, preeclampsia, or eclampsia) (yes; no) were examined. Race/ethnicity was identified as a potential effect modifier ($p = 0.0445$). Multiple logistic regression analysis stratified by race/ethnicity was conducted, providing adjusted odds ratios with corresponding 95% confidence intervals.

Results: Overall, 10.8% of women reported depression before pregnancy, and 7.3% had PIH. After adjusting for confounders, women with prepregnancy depression had a modestly higher odds of having PIH compared to women without prepregnancy depression (AOR: 1.16, 9 5% CI: 1.03, 1.30). However**,** when stratified by race/ethnicity, the association between prepregnancy depression and PIH was found to be significant for non-Hispanic Whites only. The odds of PIH was 27% higher for non-Hispanic White women who had prepregnancy depression compared to women of the same racial/ethnic category without prepregnancy depression (AOR: 1.27, 95% CI: 1.11, 1.42). No significant differences in risk were observed in the other racial/ethnic categories. Older maternal age, lower maternal education, primiparity, previous preterm birth, and prepregnancy diabetes were identified as potential risk factors for PIH.

Conclusions: Women who have had depression before pregnancy are significantly more likely to have PIH compared to women who do not have prepregnancy depression. Further, the odds of PIH is significantly high specifically among non-Hispanic White women experiencing prepregnancy depression compared to those with no such history. Public health professionals and health care providers should be aware of these findings and utilize the information in risk profiling, screening, early detection and intervention in women at risk of PIH.

Introduction

Pregnancy induced hypertension (PIH) is defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg in pregnant women with the clinical manifestation usually occurring late in pregnancy and receding after delivery of the fetus and refers to one of four conditions: pre-existing hypertension, gestational hypertension and preeclampsia, pre-existing hypertension plus superimposed gestational hypertension with proteinuria and unclassifiable hypertension.[52] For the current study, the term PIH is restricted to new development of hypertensive disorder in pregnant women who have no prior history of hypertension and therefore, exclude chronic or pre-existing hypertension and include gestational hypertension, preeclampsia and eclampsia.[51] PIH is the single leading cause of maternal mortality [3,52] and a major contributor to prematurity.[2] Furthermore, PIH is one of the most frequent causes of maternal and neonatal morbidity, complicating up to 10% of all pregnancies in the U.S.[3] In last two decades, the incidence of gestational hypertension and preeclampsia has increased significantly, whereas incidence of eclampsia has decreased.[3,12] The decline in incidence of eclampsia could be a treatment effect and an indication of survival. However, the reasons for the rise in the incidence of gestational hypertension and preeclampsia are not well explored. The rise in gestational hypertension and preeclampsia has serious health consequences for the expectant mother and fetus, along with financial ramification on the U.S. health care system.[11,13,14] Changes in a woman's lifestyle and characteristics altering certain psychosocial factors leading to poor mental health status may have contributed to the rise of gestational hypertension and preeclampsia in the recent decades in the U.S.

Depression is one of the most common mental health disorders in the United States. According to the National Institute of Mental Health, the twelve months prevalence of major depressive disorder among U. S. adult was 6.7% in 2015.[120] Lifetime major depression have been

reported to be twice in women (11.7%) compared to men (5.6%) in the US.[31] Further, prevalence of depression is higher among younger individuals compared to older people. In 2015, the rate of major depressive episode among U.S adult between the ages of 18 to 24 yrs. was 10.3% compared to 4.8% among individuals 50 yr. and above.[32] The high prevalence of depression among women and younger age group suggest that women of reproductive age could be at high risk for prepregnancy depression.

Depression is associated with hypertension and cardiovascular diseases in women [33,121-125] and therefore, might be a potential risk factor for PIH. For example, poor mental health status associated with depression may lead to hypertension in women through chronic stress [122-125] and prepregnancy hypertension is a known risk factor for PIH.[30,44] Further, a growing body of literature suggests that depression may contribute to the pathogenesis of cardiovascular disease,[34,126-129] specifically in premenopausal women, through depression-induced disruptions in ovulatory cycling,[122] changes in the immune system and dysregulation of the autonomic nervous system,[129] or serotonin-mediated platelet activation and coronary artery vasoconstriction;[127] and cardiovascular diseases share similar pathophysiological features, such as endothelial dysfunction, platelet dysfunction and sympathetic over-activity, with preeclampsia, one of the PIH.[44] Furthermore, prepregnancy depression is a major risk factor for antenatal depression [130] and antenatal depression was found to be significantly associated with PIH in previous studies.[131,132] Further, several studies proposed systemic inflammation and oxidative stress to be the factors possibly involved in the pathogenesis of preeclampsia[133,134] and markers for these factors are increased in patients with depression.[135-137]

Another factor that is associated with both depression and PIH is race/ethnicity. Depression disproportionately affects racial/ethnic minorities. According to previous studies,

non-Hispanic Blacks are 30% more likely to report having serious psychological distress than non-Hispanic Whites [138] and Hispanics have higher rates of depressive symptoms than non-Hispanic Whites.[139] Additionally, non-Hispanic Blacks have a higher rate of severe depressive symptoms (4.1%) compared to non-Hispanic Whites (2.6%).[138] Plethora of literature showed major depression to be more frequent among members of racial/ethnic minority groups than among Whites.[140-142] In a contrast, other studies reported the prevalence of depression to be significantly higher in Whites than in Blacks and Hispanics.[143,144] Similar to depression, the prevalence of PIH varies by race/ethnicity too. For example, according to a previous study done by National Institutes of Health, the odds of PIH is significantly higher in non-Hispanic blacks, while Hispanic women and Asian/Pacific Islanders have an overall decreased risk, compared to non-Hispanic whites.[145] Non-Hispanic black women were consistently found to have an increased risk of hypertension during pregnancy in previous studies.[146-152] An increasing trend of racial/ethnic disparity in PIH rates was observed in New York State in a recent study.[23] Therefore, it is possible that race/ethnicity may confound or modify the association between prepregnancy depression and PIH.

Studies that examined the association between depression and PIH mostly focused on depression during pregnancy.[131,132] One study that examined the relationship between prepregnancy depression/anxiety symptoms and hypertensive disorder of pregnancy included chronic hypertension and revealed that the observed association between prepregnancy depression or anxiety symptoms and hypertensive disorders during pregnancy were driven primarily by chronic hypertension.[46] More studies are needed to take into consideration the exclusion of chronic hypertension, a significant risk factor for PIH, to find the true association

between prepregnancy depression and PIH. The current study excludes women with chronic hypertension.

The adverse outcomes associated with PIH can be prevented or ameliorated through early detection and intervention in the risk population. Knowledge about the relationship between maternal prepregnancy depression and PIH and the racial/ethnic disparities in this relationship may aid in early detection of the at-risk population and help to establish effective interventions for PIH during the preconception and early prenatal period. Therefore, the aim of the current study is to examine the association between prepregnancy depression and PIH and to determine the role of maternal race/ethnicity in this association.

Materials and Methods

Data used for the current study come from the National Pregnancy Risk Assessment Monitoring System (PRAMS Phase 6 and 7: 2009 -2015) survey consisting of 249,983 participants. However, the current study required additional birth certificate variables named 'Years since last live birth', 'Date of last live birth', Clinical estimate of gestational age', 'Birthweight', and 'Number of prenatal care visits' and approvals to release those additional birth certificate variables to be added to the PRAMS dataset were received from 20 states out of 47 participating states. The PRAMS is a surveillance program conducted by the Centers for Disease Control and Prevention (CDC) in collaboration with state health departments.[43] Each year, between 1,300 and 3,400 women, who have had a recent live birth, are sampled from the respective state's birth certificate file. A standardized data collection methodology and a complex multistage sampling design is utilized and appropriate sampling, nonresponse, and non-coverage weights are applied. Women from minority groups and at-risk population are oversampled for proper analysis. More detailed information on the methodology are available elsewhere.[43] The

PRAMS study protocol for this study was approved by participating states and the Centers for Disease Control and Prevention Institutional Review Board.

Study Sample, Inclusion and Exclusion Criteria

Representative samples of women from 20 states participating in PRAMS survey who delivered a singleton live birth in the years of 2009 to 2015 were included in this study (N=145,870). The current study excluded women with multiple pregnancies (twin, triplets, etc.) (n=6,444 (4.4%)),[44] hypertension prior to pregnancy (n=5,301 (3.6%)),[30,44] and participants with invalid responses to outcome and exposure variable (n=44,139 (31.5%)). The final sample size for the analysis was 89,986.

Operational Definition of Outcome

The outcome variable PIH was defined as a binary variable based on a birth certificate variable that was included in the PRAMS data. Information on six risk factors in the current pregnancy are separately identified on the birth certificate in a checkbox format (yes, no). One of these six risk factors is hypertension during this pregnancy. PIH was determined using this birth certificate variable that included either prepregnancy - (Chronic) (Hypertension diagnosed prior to the onset of this pregnancy) or Gestational - (PIH, preeclampsia, eclampsia) (Hypertension diagnosed during this pregnancy). Women who were checked as "yes" to this variables were categorized as "yes" to PIH and women who were checked as "no" to this variable were categorized as "no" to PIH. Women with hypertension diagnosed prior to this pregnancy were excluded from the analysis using a PRAMS questionnaire variable, restricting the definition of PIH for this analysis to hypertension diagnosed during this pregnancy only.

Operational definition of exposure

Exposure of interest, preepregnancy depression was determined based on one item on the PRAMS survey questionnaire that asked women "*Before* you got pregnant with your new baby, did a doctor, nurse, or other health care worker tell you that you had any of the following health conditions?" One of the answer options was depression (yes, no). This option was used to create a dichotomous variable indicating prepregnancy depression; "Yes" if the respondent answered "yes" to that option and "No" if the respondent answered "no" to that option.

Operational definition of race/ethnicity

Based on previous literature, race/ethnicity was assessed as a potential confounder or effect modifier,[138-151] Race/ethnicity was determined using two birth certificate variables that were included in PRAMS dataset; "Hispanic" (yes, no) and "Maternal race" (Asian, Black, White, American Indian, Chinses, Japanese, Filipino, Hawaiian, Alaska native, other non-White, other, mixed race). Using these two variables, race/ethnicity for the current analysis was categorized into non-Hispanic White, non-Hispanic Black or African American, non-Hispanic American Indian or Alaska Native, non-Hispanic Asian, non-Hispanic Hawaiian or non-White others, and Hispanic or Latino in accordance with the standards for reporting data according to United States Census Bureau.[153]

Operational definition of potential Covariates

Based on previous literature review [32,44, 46,47],[130-132,135,149,152,] and DAG [154], several additional factors were assessed as potential confounders, moderators, or mediators in the association between prepregnancy depression and PIH. (Figure 4-1). These included sociodemographic factors: maternal age (<18, 18-24, 25-29, 30-34, 35+ years), maternal education (less than high school, high school, some college, bachelor's degree or higher), marital status (married, not married), and household income (<US$20,000; US$20,000-US$34,999;

>US$35,000- US$49,999; US$50,000+); health care access and utilization factors: insurance status before pregnancy (private insurance, Medicaid/public insurance, no insurance), adequacy of prenatal care utilization (Kotelchuck index: inadequate, intermediate, adequate, adequate plus) and residence (urban, rural); substance use/health behavioral factors: alcohol use in last 2 years (yes, no), smoking in last 2 years (yes, no); psychosocial factor: number of stressors during 12 months prior to childbirth (none, 1 or 2, 3-5, 6+); and reproductive factors and pregnancy history: parity (number of previous live births) (0, 1, 2+), previous preterm birth (yes, no), prepregnancy body mass index (BMI) (underweight: >18.5, normal weight: 18.5-24.9, overweight: 25.0 – 29.9, obese: ≥30.0 kg/m^2), prepregnancy diabetes (yes, no), and gestational diabetes (yes, no).

Statistical Analysis

All baseline characteristics were summarized using percentages. Descriptive statistics was generated to assess the distribution of characteristics among participants by prepregnancy depression and by PIH using Chi square tests. Bivariate regressions analysis provided crude odds ratios and 95% confidence limits/intervals determining the factors associated with PIH. Multicollinearity was tested for the covariates using VIF.[90] Multiple logistic regression models provided adjusted odds rations and their 95% confidence intervals determining the associations between prepregnancy depression and PIH. Based on literature review, several variables, including stress during pregnancy, prepregnancy BMI, adequacy of prenatal care utilization, prepregnancy diabetes, and gestational diabetes were assessed for mediation effects.[2,120,126-128,130,132,155,156] Possible effect modification by race/ethnicity was assessed using an interaction term between prepregnancy depression and race/ethnicity and log likelihood ratio test. Full model with the interaction term and reduced model without the interaction term were compared using the likelihood ratio test where $p<0.05$ was considered a significant difference between

models. Further, based on literature review, parity and prepregnancy stress were assessed for effect modification.[132,157] Significant interactions ($p<0.05$) were retained in the model and the results were stratified by the effect modifiers for reporting. Race/ethnicity was further assessed for confounding effect using the 10% change-in-estimate method.[92] Following assessment for mediation and effect modification, a parsimoniously adjusted regression model was analyzed adjusting for variables that were identified as confounders using the 10% change-in-estimate method and literature review. Bonferroni correction method for multiple comparison tests was performed and overall adjusted level of significance for stratified analysis was set to a p value of 0.01.[158] All analyses were conducted in SAS 9.4 to account for the complex survey design.

Results

Majority of the study population were age 25 years or older, married, had a high school or greater education level and reported a household income of $20,000 or more per year (Table 4-1). Table 1 presents characteristics of the study population, overall and by prepregnancy depression and by PIH. Nearly 66% women were non-Hispanic White, 11% non-Hispanic Black, 2% American Indian or Alaskan Native, 4% Asian, 3% Hawaiian or non-White others, and 14% were Hispanic. Overall, 10.8% of women reported being diagnosed with depression before their most recent pregnancy. Percentage of women who were unmarried, on Medicaid or public insurance, had lower income or education, had history of smoking, drinking alcohol, or six or more stressors in life, was higher among women with prepregnancy depression compared to those with no such diagnosis. Further, women with prepregnancy depression had a higher percentage of underweight or obese women and women with history of preterm birth, prepregnancy diabetes, and gestational diabetes than women without prepregnancy depression.

The prevalence of prepregnancy depression was 11.3% in non-Hispanic Whites, 7.3% in non-Hispanic Blacks, 11.6% in American Indian or Alaskan Native, 3.1% in Asians, 11.6% in Hawaiian or non-White others, and 6.1 % in Hispanics (not shown in table). Rao-Scott Chi-square tests indicated a statistically significant association between prepregnancy depression and maternal age, maternal race/ethnicity, maternal education, marital status, household income, insurance status before pregnancy, adequacy of prenatal care utilization, smoking, and drinking alcohol before pregnancy, and stress during pregnancy. Prepregnancy depression was further found to be significantly associated with parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, and gestational diabetes.

Approximately seven percent of the study participants had PIH (Table 4-1). The prevalence of PIH was significantly higher among women age 35 years or more, who were unmarried, obese or overweight, had lower education, inadequate or adequate plus prenatal care utilization, and history of smoking or drinking alcohol. Further, women who were nulliparous and had history of preterm births, prepregnancy diabetes or gestational diabetes had a significantly higher prevalence of PIH. The prevalence of PIH was highest among non-Hispanic Black (7.4%) and lowest in Asian women (3.5%) (p –value <.0001).

Figure 4-2 shows the unadjusted differences in the prevalence of PIH by prepregnancy depression and race/ethnicity. Prevalence of PIH was highest in non-Hispanic White women with prepregnancy depression (6.6%, 95% confidence interval (CI): 5.1% - 5.7%), and lowest in Asian women with no prepregnancy depression (3.4%, 95% CI: 3.1% - 4.5%).

In unadjusted and unstratified logistic regression analysis, there was a significantly increased likelihood of PIH for women who were diagnosed with prepregnancy depression compared to women who did not have prepregnancy depression (crude odds ratio (COR): 1.36,

95% CI: 1.22, 1.51) (Table 4-2). Income was found to be highly correlated with maternal education and insurance status and therefore was removed from further analysis. Prepregnancy BMI was identified as a potential mediator because prepregnancy depression predicted prepregnancy BMI significantly and prepregnancy BMI predicted PIH significantly and there was a significant difference between the odds ratios for the full model with prepregnancy BMI (adjusted odds ratio (AOR): 0.92, 95% CI: 0.83, 0.99) and reduced model without it (AOR: 1.15, 95% CI: 1.02, 1.29); therefore prepregnancy BMI was removed from further analysis. Similarly, adequacy of prenatal care utilization was identified as a potential mediator and therefore was removed from further analysis. Gestational diabetes was not identified as a mediator in the assessment for mediation effect; however it was not included in the adjusted analyses due to ambiguity in the temporal sequence between gestational diabetes and PIH in the cross-sectional PRAMS data.

In the bivariate logistic regression analysis of race/ethnicity and PIH, compared to non-Hispanic White women, the odds of PIH was significantly higher for non-Hispanic Black women (COR: 1.27, 95% CI: 1.02, 1.34) and lower for Non-Hispanic Asian (COR: 0.63, 95% CI: 0.50, 0.78) and Hispanic women (COR: 0.71, 95% CI: 0.62, 0.81) (not shown in table). However, no significant associations were observed between other racial/ethnic categories and PIH. Further, race/ethnicity was identified as an effect modifier in the association between prepregnancy depression and PIH using the log likelihood ratio test (p=0.0445) and therefore, a stratified analysis by race/ethnicity was conducted. However, race/ethnicity did not make a more than 10% change in estimate in the assessment of confounding effect.

For the adjusted model, after adjusting for maternal age, maternal education, marital status, smoking, alcohol use, parity, previous preterm birth, and prepregnancy diabetes, women

with prepregnancy depression were 1.16 times as likely to have PIH as women without prepregnancy depression (AOR: 1.16, 95% CI: 1.03, 1.30) (Table 4-2). Further, older maternal age, lower maternal education, primiparity, previous preterm birth, and prepregnancy diabetes were identified as significant risk factors for PIH in the adjusted analysis. In the analysis stratified by race/ethnicity, the unadjusted model showed significant positive association between prepregnancy depression and PIH for non-Hispanic White women (COR: 1.32, 95% CI: 1.14, 1.53) (Table 4-3); however this association attenuated but remained significant after adjusting for potential confounders (AOR: 1.27, 95% CI: 1.11, 1.4). No significant differences in PIH by prepregnancy depression were observed among other categories of race/ethnicity.

Discussion

The current study found a small but significant independent association between prepregnancy depression and PIH. Women who had been diagnosed with depression prior to their most recent pregnancy were more likely to have pregnancy induced hypertension during that pregnancy compared to women without prepregnancy depression. Findings from the study further revealed racial/ethnic differences in the association between prepregnancy depression and PIH. Among the non-Hispanic White study population, the odds of PIH was significantly higher for women with history of prepregnancy depression compared to women without such history. For the non-Hispanic Asian, and non-Hispanic Hawaiian or non-White other women, a direct but non-significant association was observed between prepregnancy depression and PIH; whereas an inverse but non-significant association was observed for the non-Hispanic Black, non-Hispanic American Indian or Alaskan Native, and Hispanic women.

Findings from this study showed that approximately seven percent of the women in the study had PIH and about eleven percent had depression prior to pregnancy. These findings are

consistent with previous literature reporting prevalence of PIH to be 6% to 10%[3,155,156] and prevalence of lifetime major depression to be 11.7%[31] in the U.S women. Further, the racial and ethnic differences in the odds of PIH found in the current study showing higher odds of PIH in the non-Hispanic Black women and lower in the Hispanic and non-Hispanic Asian women, compared to non-Hispanic White women, are also consistent with previous literatures.[146,147] However, the result in the current study showing prevalence of prepregnancy depression to be higher in non-Hispanic White women compared to racial-ethnic minority groups may be in contrast with several previous literatures that revealed a higher rate of major depression in the racial-ethnic minority groups.[138-142] This discrepancy can be explained by the fact that the prevalence rates in those prior studies involved overall adults and diagnosis of major depression, whereas the current study involved only women of reproductive age and the diagnosis was depression in general, not major depression specifically. Moreover, the racial/ethnic differences in prevalence of depression found in the current study is consistent with the findings of some of prior studies.[143,144] For example, a prior study by the National Health and Nutrition Examination Survey (NHANES) III reported the prevalence of major depressive disorder to be significantly higher in Whites than in African Americans and Mexican Americans.[143]

The observed relationship between prepregnancy depression and PIH could be explained by chronic stress and hypertension being associated with both prepregnancy depression and PIH. Depression is known to cause oxidative stress and systematic inflammation,[135-137] both of which are associated with chronic stress and are factors suggested to be involved in the pathogenesis of preeclampsia.[133,134] In addition, chronic stress is a known risk factor for hypertension[122-125] and prepregnancy hypertension is known to increase the risk of PIH.[30,44] PIH has been hypothesized to be a primarily a hypertensive event of pregnancy.[5] Moreover, depression before pregnancy is a

strong predictor of antenatal depression[130] and studies found antenatal depression to be associated with PIH.[131,132]

The findings in the current study could also be interpreted by cardiovascular disease being linked to both depression and PIH. Depression is an independent risk factor for[34,123] and contributor to the pathogenesis of cardiovascular diseases.[126-128] The factors that may contribute to an increased risk of cardiovascular diseases in patients with depression are smoking, inactivity, hypertension, and diabetes.[157] Further, depression in general is known to cause changes in immune and autonomic nervous system [129] and serotonin-mediated platelet activation,[127] both of which may contribute to increased risk for cardiovascular diseases.[127,129] In regards to depression in women in particular, depression-induced disruptions in ovulatory cycling has been suggested to be associated with cardiovascular disease in premenopausal women in a previous study using data from the Women's Ischemia Syndrome Evaluation (WISE).[122] PIH, on the other hand, has been hypothesized to be a primarily a hypertensive event of pregnancy[5] and involves endothelial and platelet dysfunction and sympathetic over-activity, [44] that are also present in cardiovascular diseases. Further, PIH and cardiovascular diseases share several risk factors, such as hypertension and diabetes; and have similar pathophysiology, such as endothelial damage, vasoconstriction, platelet activation, and aggregation mediated by serotonin.[157]

The findings in the current study in regards to effect modification of the association between prepregnancy depression and PIH by race-ethnicity might be somewhat in contrast with suggestions drawn from previous literatures. Previous studies mostly revealed a higher prevalence of PIH[144,145] and higher rate of major depression[138-142] in non-Hispanic Black women compared to other race-ethnicities, suggesting a higher odds of PIH with prepregnancy

depression for non-Hispanic Black women. The current study found no such statistically significant association for the non-Hispanic Black women. This could be partially explained by the inconsistency in the previous studies regarding racial ethnic disparities in the prevalence of depression. For example, in contrast to other studies, which mostly revealed higher prevalence of major depression in non-Hispanic Blacks,[138-142] some prior studies reported higher prevalence of depression in Whites compared to Blacks and Hispanics[143,144] and the current study also showed similar findings. This could also explain the finding of current study of higher odds of PIH with prepregnancy depression for non-Hispanic White women than women of racial-ethnic minority groups. Further, women of racial-ethnic minority groups might have entered the study with undiagnosed depression causing misclassification of exposure, resulting in underestimation of associations for the racial-ethnic minority groups. Prior studies suggested underdiagnoses and/or misdiagnosis of depression and other mental health disorders among racial-ethnic minority groups, mostly due to less access to and underutilization of mental health services.[144,159,160]

The major strength of the study is use of a robust population-based dataset with a large sample size. The analysis was performed using a nationally representative sample of women with live births. This allows inference to the general U.S. women population. All states in the PRAMS dataset maintain an overall response rate of at least 65% to minimize nonresponse bias and ensure representation of the population under study.[43] The outcome measure, pregnancy induced hypertension, was based on a birth certificate variable, information for which was collected directly from the medical record by a health professional using the facility worksheet; therefore can be considered valid.[45] Further, women with prepregnancy hypertension were excluded from the analysis ensuring more inclusive definition for the outcome measure. Moreover, the measure used for main exposure variable, prepregnancy depression, came from diagnosis by a health care

professional[43] and was validated in other studies.[161,162] The measures for most of the covariates used in this analysis came from birth certificate or diagnosis by a health care professional and therefore can be considered valid.[43,45] Further, the current study focused on prepregnancy depression, unlike previous studies that analyzed depression during pregnancy as a risk factor for preeclampsia. Also, this study excluded women with chronic hypertension, a significant risk factor for PIH and a potential driver of association between prepregnancy depression and PIH,[46] revealing the true association between prepregnancy depression and PIH.

Despite its strengths, the current study should be viewed in light of a few limitations. Foremost, the exposure variable, prepregnancy depression was without diagnosis of types or quantitative measures on severity. This might have caused dilution of effects of depression on PIH leading to underestimations. Further, hypertension could be one of the major explanatory factors on the causal pathway between prepregnancy depression and PIH; but women with prepregnancy hypertension had to be excluded from the current analyses to define PIH validly and inclusively, and that might have caused underestimation of the association leading to insignificant findings. Moreover, the study sample for the current study comes from 20 states, instead of all 47 states that participates in national level PRAMS survey. This might have reduced the generalizability of the inference of this study to the overall U.S. women. However, these 20 states are scattered all over the U.S. representing all four Northeast, Midwest, South, and West regions, and therefore can be considered as representative of general U.S. population. Further, the temporal relationships between exposures and outcome cannot be determined based on the cross-sectional PRAMS data; however prepregnancy depression and PIH have temporal elements to inform directionality. Moreover, information on some potential confounding factors such as previous PIH, antidepressant treatment prior to pregnancy, antihypertensive treatment,

and history of cardiovascular diseases were not available in the dataset and could not be assessed and therefore, might have affected the estimates of association. Lastlt, previous pregnancy induced hypertension is a major risk factor of pregnancy induced hypertension in the current pregnancy but it could not be assessed or excluded from the current analysis because of unavailability of information in the dataset.

This study revealed important findings that have clinical relevance. To the authors' knowledge, this is the first study to investigate the racial-ethnic disparities in the association between prepregnancy depression and PIH. The current study highlights the importance of diagnosis and intervention of depression in women of reproductive age during the preconception and early prenatal care. The findings from this study can aid in risk profiling, screening, and early detection of women at risk for development of PIH based on diagnosis of depression in preconception and early prenatal period. This would facilitate early diagnosis and proper management of PIH, thus would halt further progression to more detrimental maternal and fetal outcomes, reducing the rate of adverse birth outcomes associated with PIH. Further, knowledge gained from this study can be utilized to develop effective preventive intervention policy to improve maternal and fetal health. Knowledge gained from this study can also guide future research in etiology of PIH by adding information in understanding the factors associated with PIH.

Conclusion

The current study reveals that women with depression before pregnancy are significantly more likely to have PIH compared to women who do not have prepregnancy depression and the odds of PIH is significantly high specifically among non-Hispanic White women experiencing

prepregnancy depression compared to those with no such history. This study provides insight into the interrelationship between prepregnancy depression, race/ethnicity and PIH and proposes screening for depression during preconception period and first prenatal visit. Findings from this study suggests that screening and intervention of depression during preconception period may reduce the risk of PIH in future pregnancy. Findings further suggest that identifying the at-risk population for PIH based on racial/ethnic profiling and screening of depression during first prenatal visit may aid in early detection and intervention of PIH and thereby may prevent or ameliorate the adverse birth outcomes associated with PIH. Further research is recommended using more effective quantitative measures of depression instead of relying on self-reports, to capture the true prevalence of depression among the women of racial/ethnic minority groups in order to clarify the racial/ethnic disparities in the association between prepregnancy depression and PIH.

Table 4-1. Characteristics of the Study Population by Prepregnancy Depression and Pregnancy Induced Hypertension; PRAMS 2009-2015

	Total (N= 89,986)	**Prepregnancy Depression**		**P-value (Rao-Scott Chi^2 Test)**	**PIH (N= 6,511; 7.3%)**	**P-value (Rao-Scott Chi^2 Test)**
		Yes (N=9,693; 10.8%)	**No N=80,293; 89.2%)**			
	%	**%**			**Prevalence**	
Socio-Demographic Factors						
Maternal Age				<.0001		0.0549
<18 years.	6.6	9.4	6.3		6.1	
18 -24 years	22.2	26.7	21.6		4.8	
25-29 years	30.9	29.2	31.1		5.2	
30- 34 years	26.5	22.7	26.9		5.5	
35+ years	13.8	12.0	14.0		5.7	
Race/Ethnicity				<.0001		<.0001
Non-Hispanic White	66.2	76.2	65.1		5.5	
Non-Hispanic Black	11.2	8.3	11.5		7.4	
Non-Hispanic American Indian or Alaskan Native	1.5	1.7	1.4		5.8	
Non-Hispanic Asian	4.1	1.3	4.4		3.5	
Non-Hispanic Hawaiian & non-White others	3.0	3.6	3.0		5.6	
Hispanic	14.0	8.8	14.6		4.0	
Maternal Education				<.0001		0.0028
Less than high School	13.3	17.9	12.8		5.1	
High School	24.1	29.3	23.5		5.4	
Some College	29.2	32.9	28.8		5.9	
Bachelor's degree or higher	33.5	19.9	34.9		4.8	
Marital Status				<.0001		0.0104
Not Married	36.2	51.9	34.5		5.7	
Married	63.8	48.1	65.5		5.1	
Household Income				<.0001		0.3224
Less than $20,000	29.4	45.8	27.6		5.4	
$20,000 to 34,999	20.2	19.9	20.3		5.6	
$35,000 to 49,999	11.7	10.0	11.8		5.4	
$50,000 or more	38.7	24.3	40.3		5.0	
Healthcare Access and Utilization factors						
Insurance before Pregnancy				<.0001		0.6358
Private insurance	61.5	50.2	62.7		5.2	
Medicaid/Public insurance	17.4	30.6	16.0		5.4	
No insurance	21.1	19.2	21.3		5.6	

Adequacy of Prenatal Care Utilization				<.0001		<.0001
Inadequate	12.0	12.3	12.0		4.5	
Intermediate	12.5	11.5	12.6		3.4	
Adequate	48.2	43.8	48.7		4.2	
Adequate plus	27.3	32.4	26.7		8.6	
Residence				0.0715		0.9387
Rural	34.7	36.2	34.5		5.4	
Urban	65.3	63.8	65.5		5.4	
Substance Use/Health Behavioral Factors						
Smoked before Pregnancy				<.0001		0.0055
Yes	24.9	50.9	22.1		5.9	
No	75.1	49.1	77.9		5.1	
Alcohol Use before Pregnancy				<.0001		0.0063
Yes	64.5	72.9	63.6		5.6	
No	35.5	27.1	36.4		4.9	
Psychosocial Factors						
Number of Stressors during pregnancy				<.0001		0.3229
None	29.4	12.7	31.2		5.1	
1 to 2	24.2	15.8	25.1		5.2	
3 to 5	17.4	16.1	17.6		5.4	
6+	29.1	55.4	26.1		5.7	
Reproductive and Pregnancy History						
Previous Live Births				0.0003		<.0001
None	40.3	40.6	40.2		7.1	
One	32.3	29.6	32.5		3.9	
Two or more	27.4	29.8	27.2		4.0	
Previous Preterm birth: Yes	3.3	4.6	3.2	<.0001	7.8	<.0001
No	96.7	95.4	96.8		5.2	
Prepregnancy BMI				<.0001		<.0001
Underweight (<18.5)	3.6	4.2	3.6		3.0	
Normal BMI (18.5 - 24.9)	48.1	40.8	48.9		3.4	
Overweight (25.0 -29.9)	25.0	24.9	25.0		5.4	
Obese (>=30.0)	23.3	30.1	22.5		9.2	
Prepregnancy Diabetes: Yes	1.2	2.3	1.0	<.0001	12.7	<.0001
No	98.8	97.7	99.0		5.2	
Gestational Diabetes: Yes	5.1	6.2	5.0	0.0017	10.6	<.0001
No	94.9	93.8	95.0		5.0	

Abbreviations: BMI, body mass index (kg/m^2); PIH, pregnancy induced hypertension

Table 4-2. Unadjusted and Adjusted Odds Ratios of Prepregnancy Depression and Pregnancy Induced Hypertension; PRAMS 2009-2015

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Prepregnancy Depression		
Yes	1.36 (1.22, 1.51)*	1.16 (1.03, 1.30)*
No	1.00	1.00
Socio-Demographic Factors		
Maternal Age		
<18 years.	1.19 (0.98, 1.44)	0.80 (0.62, 1.02)
18 -24 years	0.93 (0.82, 1.05)	0.73 (0.63, 0.85)*
25- 29 years	1.00	1.00
30-34 years	1.06 (0.94, 1.19)	1.22 (1.07, 1.39)*
35+ years	1.15 (1.02, 1.25)*	1.34 (1.15, 1.57)*
Maternal Education		
Less than high school	1.04 (0.89, 1.21)	1.29 (1.06, 1.58)*
High school	1.11 (0.99, 1.26)	1.36 (1.15, 1.60)*
Some college	1.23 (1.10, 1.38)*	1.42 (1.24, 1.61)*
Bachelor's degree or higher	1.00	
Marital Status		
Not married	1.13 (1.03, 1.24)*	1.09 (0.96, 1.24)
Married	1.00	1.00
Substance Use/Health Behavior		
Smoked before Pregnancy: Yes	1.16 (1.04, 1.28)*	0.99 (0.87, 1.13)
No	1.00	1.00
Alcohol Use before Pregnancy: Yes	1.14 (1.04, 1.25)*	1.07 (0.95, 1.20)
No	1.00	1.00
Reproductive and Pregnancy History		
Previous Live births: None	1.72 (1.54, 1.93)*	2.22 (1.92, 2.56)*
One	0.96 (0.84, 1.09)	1.12 (0.97, 1.30)
Two or more	1.00	1.00
Previous Preterm Birth		
Yes	1.56 (1.27, 1.91)*	2.04 (1.64, 2.54)*
No	1.00	1.00
Prepregnancy Diabetes		
Yes	2.63 (2.04, 3.39)*	2.66 (1.99, 3.56)*
No	1.00	1.00

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for maternal age, education, marital status, smoking, alcohol use, parity, previous preterm birth, and prepregnancy diabetes

*Level of significance P <0.05

Table 4-3. Unadjusted and Adjusted Regression Analysis of Prepregnancy Depression and Pregnancy Induced Hypertension; Stratified by Race/Ethnicity

	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-Hispanic White		
Prepregnancy Depression		
Yes	**1.32 (1.14, 1.53)***	**1.27 (1.11, 1.42)***
No	1.00	1.00
Non-Hispanic Black		
Prepregnancy Depression		
Yes	0.93 (0.81, 1.46)	0.69 (0.63, 1.20)
No	1.00	1.00
Non-Hispanic American Indian or Alaskan Native		
Prepregnancy Depression		
Yes	0.91 (0.50, 1.77)	0.72 (0.40, 1.31)
No	1.00	1.00
Non-Hispanic Asian		
Prepregnancy Depression		
Yes	1.35 (0.39, 4.63)	1.80 (0.51, 6.52)
No	1.00	1.00
Non-Hispanic Hawaiian and Non-White Others		
Prepregnancy Depression		
Yes	1.13 (0.54, 2.34)	1.12 (0.50, 2.51)
No	1.00	1.00
Hispanic		
Prepregnancy Depression Yes	1.14 (0.92, 1.66)	0.93 (0.58, 1.49)
No	1.00	1.00

Abbreviations: OR, odds ratio; CI, confidence interval

[a] Adjusted for maternal age, education, marital status, smoking, alcohol use, parity, previous preterm birth, and prepregnancy diabetes

* $p < .01$

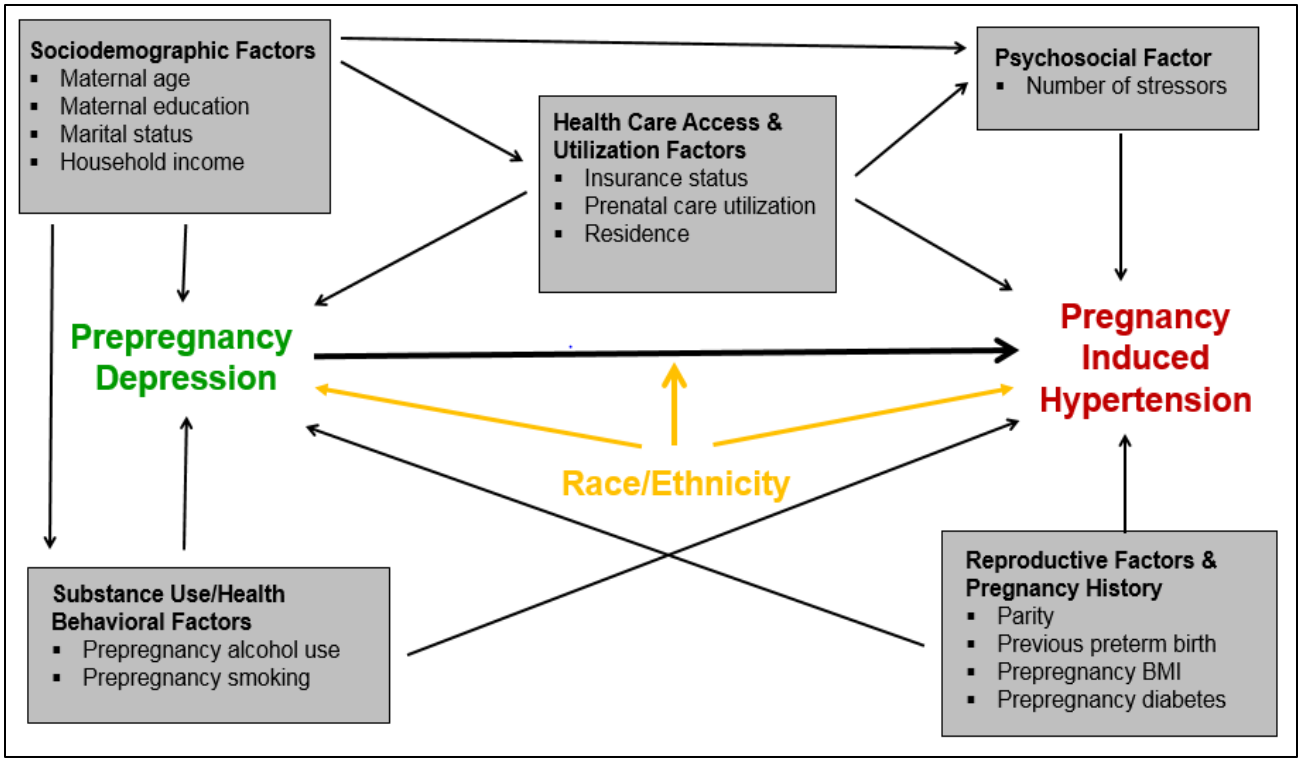

Figure 4-1. Directed Acyclic Graph (DAG) presenting risk factors, potential effect modifiers and confounding factors in the association between prepregnancy depression and pregnancy induced hypertension

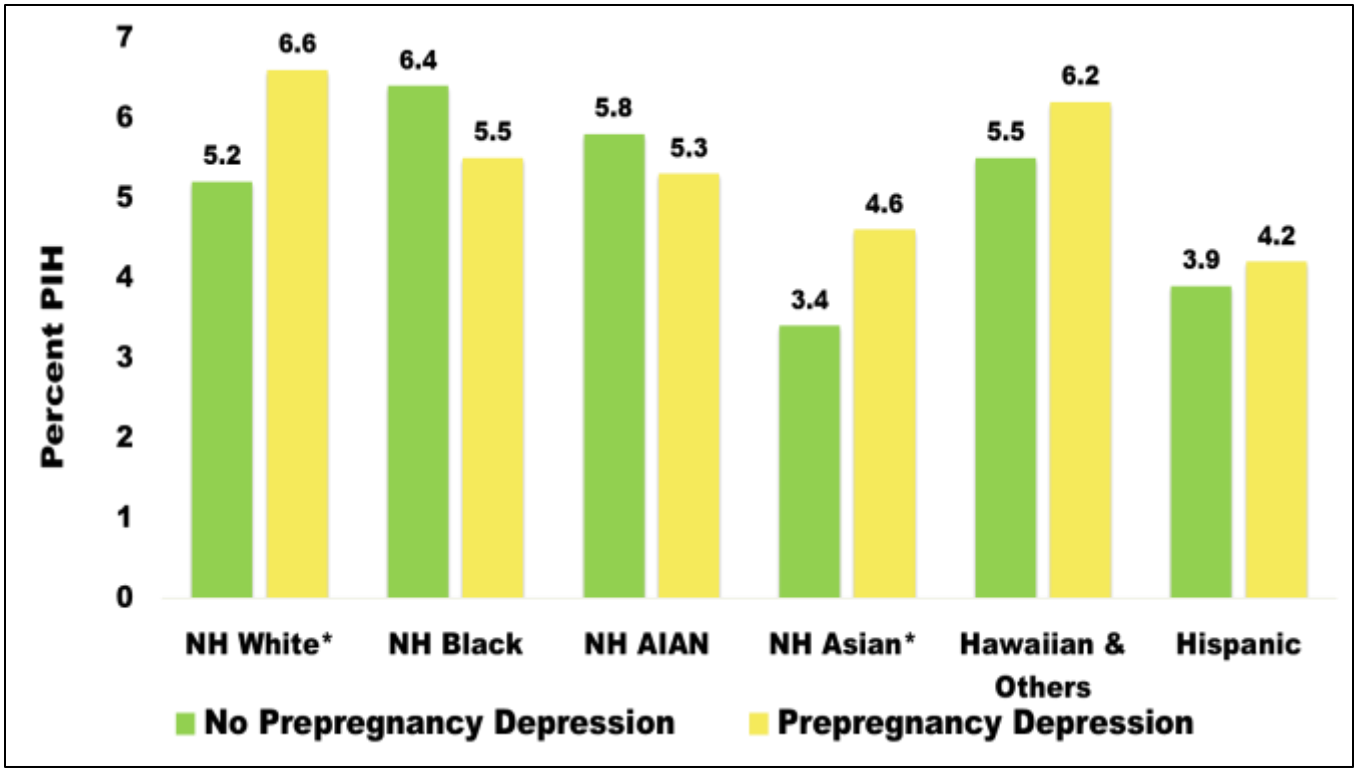

Figure 4-2. Prevalence of Pregnancy Induced Hypertension by Prepregnancy Depression across Racial/Ethnic Categories

Abbreviations: PIH, Pregnancy Induced Hypertension; NH, non-Hispanic; AIAN, American Indian Alaskan Native

Hawaiian & Others = Non-Hispanic Hawaiian and non-Hispanic non-White others

* P value <.0001

Chapter 5: Association between intimate partner violence in women before and/or during pregnancy and pregnancy induced hypertension, and the mediating effect of prenatal care utilization in this association.

Abstract

Background: Pregnancy induced hypertension (PIH), a major contributor to prematurity and maternal mortality, affects 5-10% of all pregnancies in the U.S. About 3% to 9% of pregnant women in the U.S. experience severe physical violence by an intimate partner posing additional risks for poor maternal health and pregnancy outcomes. Intimate partner violence (IPV) around the time of pregnancy may reduce the utilization of prenatal care by the abused women and thereby, may increase the risk of PIH for these women. The association between IPV around the time of pregnancy, utilization of prenatal care and PIH is under investigated. Knowledge about these relationships may facilitate early detection of women at risk for adverse pregnancy outcomes. Therefore, the objective of this study is to evaluate the association between IPV around the time of pregnancy and PIH and the mediating role of prenatal care utilization in this association.

Methods: The current study analyzed data derived from Phase 6 and 7 of the National Pregnancy Risk Assessment Monitoring System (PRAMS, year 2009-2015). The data consist of participants with recent singleton live births without prepregnancy hypertension (n = 64,618). IPV before and/or during pregnancy (yes; no), prenatal care utilization (Kotelchuck index: inadequate, intermediate, adequate, adequate plus), and PIH (gestational hypertension, preeclampsia, or eclampsia) (yes; no) were examined. Structural equation model (SEM) path analyses were performed in MPlus program and path coefficient estimates of total, direct and indirect effects of IPV on PIH were generated. A joint significance test using the percentile bootstrap was conducted to test for the indirect/mediating effect.

Results: The prevalence of PIH was 7.3%; 4.1% reported IPV before and/or during pregnancy, and the average number of prenatal care visit by the study participants was 10.9 (SD $\pm$4.03). In the adjusted path analyses, the indirect effect of IPV before and/or during pregnancy on PIH showed that women with history of IPV had a 2% reduced odds of having PIH through utilization of PNC compared to women without history of IPV (AOR:0.98, 95% CI:0.97, 0.99; p= 0.045). Further, the likelihood of higher order of prenatal care utilization was 10% less for women with history of IPV compared to women with no such history (AOR: 0.90, 95% CI: 0.89, 0.91; P=0.006)) and with one order increase in Kotelchuck index of prenatal care utilization, the odds of PIH increased by 17% after controlling for the effect of IPV and other potential confounders in the adjusted analysis (AOR: 1.17, 95% CI: 1.16, 1.18; p<0.0001).

Conclusions: IPV around the time of pregnancy has no significant total or direct effect on PIH. However, IPV has a significant, though negligible, indirect effect on PIH through utilization of PNC. Further, women who experience IPV before and/or during pregnancy are significantly less likely to utilize PNC adequately compared to women who do not have such experience. It is important that health professionals focus on utilizing available screening tools to assess IPV during first prenatal care visit and provide or refer women who screen positive to intervention services and ensure adequate prenatal care visits for these women to reduce the additive risk of adverse pregnancy outcomes in these women.

Introduction

Pregnancy induced hypertension (PIH) is one of the most frequent causes of maternal and neonatal morbidity, complicating up to 10% of all pregnancies in the U.S.[3] The incidence of gestational hypertension and preeclampsia has increased significantly in last two decades, whereas incidence of eclampsia has decreased.[3,12] However, the reasons for the rise in the incidence of gestational hypertension and preeclampsia are not well explored. Changes in a woman's lifestyle and characteristics altering certain psychosocial factors, leading to chronic stress and inadequate utilization of prenatal care may have contributed to the rise of gestational hypertension and preeclampsia in the recent decades in the U.S. Intimate partner violence (IPV) around the time of pregnancy is associated with poor maternal health and pregnancy outcomes;[37-40,163] thus might be associated with PIH directly due to chronic stress or indirectly through inadequate utilization of prenatal care.

In the U.S., an estimated 22% of women experience severe physical abuse and 25% experience sexual violence by an intimate partner during their lifetime.[35,164] IPV is defined as physical violence, sexual violence, stalking, and/or psychological aggression (including coercive tactics) by a current or former intimate partner (i.e., spouse, boyfriend/girlfriend, dating partner, or ongoing sexual partner).[35] IPV has been shown to affect women's physical and mental health.[165,166] About three to nine percent of pregnant women in the U.S. experience IPV in the form of severe physical violence.[36] IPV around the time of pregnancy poses additional risks for poor maternal health and pregnancy outcomes, such as low birth weight, preterm births, induced abortions, unintentional pregnancy loss, infection, inadequate weight gain, and fetal injury.[37,39,40,163] Further, a few studies suggest an association between IPV around the time of pregnancy and preeclampsia,[36,48] a form of PIH; however, these studies considered

preeclampsia only, not other forms of PIH. Also, these studies analyzed IPV during pregnancy only, not before pregnancy, which would have provided better temporal sequence of events between IPV and PIH.

IPV around the time of pregnancy may have a direct effect on development of PIH. IPV may increase the risk of PIH due to chronic stress. Women experiencing IPV before and during pregnancy can have elevated levels of mood and anxiety disorders and chronic stress.[49,167-169] IPV is a known social and environmental stressor that can adversely affect the neuroendocrine and physiological changes integral to pregnancy[168,170] and thus may contribute to increased risk of PIH. Chronic stress has been demonstrated to increase susceptibility to disease via changes in endocrine and immune functioning.[170,171] Moreover, experiencing IPV has been associated with cardiovascular conditions including hypertension in women[172] and chronic hypertension in women is a known risk factor of PIH.[3,72,73]

Another important factor, utilization of prenatal care could be a mediator in the association between IPV around the time of pregnancy and PIH. The main purpose of prenatal care (PNC) is to screen and manage health conditions that could be detrimental to the wellbeing of the mother and fetus.[173] Early detection and proper intervention of hypertension during prenatal care can prevent the progression of the disorder to further detrimental conditions, such as preeclampsia, eclampsia and HEELP (hemolysis, elevated liver enzymes and low platelet count) syndrome and can reduce the adverse birth outcomes associated with these conditions.[174]

Adequacy of Prenatal Care Utilization (APNCU)

The utilization of prenatal care is frequently estimated by Kotelchuck index or the Adequacy of Prenatal Care Utilization (APNCU) Index that uses three elements; the time of initiation of prenatal care, the total number of prenatal visits received, and the expected number

of prenatal visits for that time period.[175,176] Utilization of prenatal care is associated with many factors, such as maternal age, education, race/ethnicity, socioeconomic status, perceived risk, and parity.[177,178] and can be associated with IPV during pregnancy too. Insurance status and access to health care services are directly associated with utilization of prenatal care [179,180] and previous studies have reported having Medicaid or no insurance to be associated with IPV.[181,182] Furthermore, IPV during pregnancy was found to be linked to inadequate utilization of prenatal care by the abused women due to delayed entry and under-attendance in several studies.[183-185] Moreover, utilization of prenatal care can be independently associated with PIH. Adequate utilization of prenatal care has been shown to decrease the risk of PIH.[177,178] Delayed entry into or under-attendance of prenatal care by the IPV victim women may increase the likelihood of missing the diagnosis and treatment of early symptoms of PIH by the health care provider and thereby may increase the risk of severe form of PIH.[180] Thus, utilization of prenatal care could be on the causal pathway between IPV during pregnancy and PIH.

Little is known about the role of prenatal care utilization in the relationship between IPV and PIH. Knowledge about the mediating role of prenatal care utilization in the relationship may facilitate early detection of women at risk and intervention in relation to IPV and prenatal care utilization. The knowledge thereby may contribute to policy making in the reduction of adverse pregnancy outcomes in relation to PIH. Further, to the knowledge of the authors, the association between IPV around the time of pregnancy and PIH is under investigated. Therefore, the objective of this study is to evaluate the association between IPV in women around the time of pregnancy and PIH and the role of utilization of prenatal care as a mediator in this association.

Materials and Methods

The National Pregnancy Risk Assessment Monitoring System (PRAMS Phase 6 and 7, year 2009 – 2015) survey data was analyzed. The PRAMS is a surveillance program conducted by the Centers for Disease Control and Prevention (CDC) in collaboration with state health departments that collect national data on maternal behaviors, attitudes and experiences before, during, and shortly after pregnancy.[43] A standardized data collection methodology which utilizes a mixed mode of data collection is employed. Mother's responses are then linked to the corresponding birth certificate data. A complex multistage sampling design is utilized and appropriate sampling, nonresponse, and non-coverage weights are applied. Additional information on PRAMS methodology can be found elsewhere.[43]

Study Sample Inclusion and Exclusion Criteria

The study sample for this analysis (n = 64,618) included all women participating in PRAMS survey who delivered a singleton live birth in the years of 2009 to 2015. The current study excluded women with multiple pregnancies (twin, triplets, etc.) (n=3,575 (4.4%)),[44] hypertension prior to pregnancy (n=3,006 (3.7%)),[3,72,73] and participants with invalid responses to outcome, mediator and exposure variables (n=38,676 (47.6%)).

Operational Definition of Outcome (Endogenous variable)

Pregnancy induced hypertension (PIH), the outcome, was defined as a binary variable based on a birth certificate variable that was included in the PRAMS data. This birth certificate variable included either prepregnancy - (Chronic) (Hypertension diagnosed prior to the onset of this pregnancy) or Gestational - (PIH, preeclampsia, eclampsia) (Hypertension diagnosed during this pregnancy). Women who were checked as "yes" to this variables were categorized as "yes" to PIH and women who were checked as "no" to this variable were categorized as "no" to PIH. Women with hypertension diagnosed prior to this pregnancy were excluded from the analysis

using a PRAMS questionnaire variable, restricting the definition of PIH for this analysis to hypertension diagnosed during this pregnancy only.

Operational Definition of Major predictor variable (Exogenous variable)

Intimate partner violence before and/or during pregnancy, the main predictor variable, was assessed using the survey questions that asked women whether their husband or partner "push, hit, slap, kick, choke, or physically hurt [the respondent] in any way," 12 months before or during pregnancy with their most recent child.[43] A binary variable (0= *no IPV before and/or during pregnancy*, 1= *IPV before and/ or during pregnancy)* was created to indicate whether women experienced IPV before and/or during their most recent pregnancy according to the convention of prior studies.[187,188]

Operational Definition of Potential Mediator

Utilization of prenatal care was assessed using the Kotelchuck Index,[176] a two part index that combines independent assessments of the timing of prenatal care initiation (month 1 to 9) and the frequency of visits received after initiation (the actual number of visits).[176] Kotelchuck Index, the measure for adequacy of received services, is the ratio of the actual/observed number of visits to the expected number of visits for the duration of eligible care according to the America College of Obstetricians and Gynecologists (ACOG) prenatal care visitation standards adjusted for the gestational age at initiation of care and gestational age at delivery.[176] Kotelchuck Index is categorized into Inadequate (less than 50% of expected visits), Intermediate (50%-79%), Adequate (80%-109%), and Adequate Plus (≥110%).[176] For the current study, Kotelchuck Index was analyzed as categorical variable. Further, for the sensitivity analysis, number of total PNC visits was analyzed as a continuous variable.

Operational Definition of Potential Covariates

Based on previous literature [3,35,37-39,44,181,182] and DAG [154], potential covariates that might mediate, moderate, or confound the relationship between intimate partner violence around the time of pregnancy, PNC utilization, and PIH were considered (Figure 5-1 & 5-2). These included sociodemographic factors: maternal age (<18, 18-24, 25-29, 30-34, 35+ years), maternal race (non-Hispanic white, non-Hispanic black, non-Hispanic other, Hispanic), maternal education (less than high school, high school, some college, bachelor's degree or higher), marital status (married, not married), and household income (<US$20,000; US$20,000-US$34,999; >US$35,000- US$49,999; US$50,000+); health care access and utilization factors: insurance status before pregnancy (private insurance, Medicaid/public insurance, no insurance) and residence (urban, rural); substance use/health behavioral factors: alcohol use in last 2 years (yes, no), smoking in last 2 years (yes, no); psychosocial factor: number of stressors during 12 months prior to childbirth (none, 1 or 2, 3-5, 6+); and reproductive factors and pregnancy history: parity (number of previous live births) (0, 1, 2+), previous preterm birth (yes, no), prepregnancy diabetes (yes, no), prepregnancy body mass index (BMI) (underweight: >18.5, normal weight: 18.5-24.9, overweight: 25.0 – 29.9, obese: ≥30.0 kg/m^2), pregnancy weight gain (<11 lbs., 11 to 20 lbs., 21 to 30 lbs., 31 to 40 lbs., >40 lbs.), and gestational diabetes (yes, no).

Statistical Analysis

Descriptive statistics was generated using percentages to assess the distribution of characteristics among the study participants, overall and by IPV before and/or during pregnancy and by PNC utilization. A chi-square test was used to compare groups of women based on IPV and PNC utilization status. Correlation matrix was produced to assess the linear relationships between the study variables. Multicollinearity was tested for the covariates using the variance

inflation factor (VIF).[90] Based on literature review, pregnancy weight gain, depression and stress during pregnancy were identified and therefore were tested for potential mediation for different pathways.[38,49,167-172] Further, race/ethnicity, marital status, and parity were identified as potential effect modifier for different pathways in the literature review and therefore were tested for effect modification.[1,44,181,182] Variables were included in the models as confounders if their presence resulted in a greater than 10% change in the estimate.[92]

Thereafter, a full mediation model (Figure 5-3) was analyzed using structural equation modeling (SEM) path analysis to evaluate the total and direct effect of IPV on PIH and the mediation effect of utilization of prenatal care on the association between IPV and PIH. The current model was identified due to the recursive rule that was sufficient for identification. Further, the current model was just-identified with $df_m = 0$ and indicated a satisfied t-rule. Model fit was determined based on Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and non-significant chi-square value.[189] To test for the mediation (indirect) effects, the product of the coefficients was tested utilizing the percentile bootstrap.[189,190] A maximum likelihood estimation with robust standard errors was used to correct for the non-normal outcome. The total effect and mediation ratio was calculated to help describe the proportion of the relationship explained by the indirect effects. A sensitivity analysis was performed using PNC utilization as a continuous variable (total number of prenatal visits). Descriptive statistics was calculated using SAS version 9.4 statistical software (SAS, Cary, NC), while structural equation modeling analyses was performed in Mplus program.[191]

Results

Overall, 7.3% had PIH during their most recent pregnancy, 4.1% reported IPV before

and/or during pregnancy and the average number of prenatal care visit by the study participants was about eleven (mean = 10.9, standard deviation (SD) ±4.03)). Majority of women reporting IPV before and/or during pregnancy were 29 years old or younger, not married, had no college education, had household income less than $20,000 a year, had Medicaid/public insurance or no insurance, were smokers, and had six or more stressors in life during pregnancy (Table 5-1). IPV before and/or during pregnancy was significantly associated with sociodemographic factors including maternal age, race/ethnicity, education, marital status, and household income; healthcare access factors such as insurance before pregnancy and prenatal care utilization; substance use including smoking and drinking alcohol; psychosocial factor such as stressors in life; and reproductive and pregnancy related factors including parity, prepregnancy BMI and pregnancy weight gain. The prevalence of PIH was significantly higher among women less than 18 years of age or age 35 years or more, who were unmarried, obese or overweight, had lower education, inadequate or adequate plus prenatal care utilization, and history of smoking or drinking alcohol. Further, women who were nulliparous, had history of preterm births, prepregnancy diabetes, or gestational diabetes, and gained more than 40 lbs. during pregnancy had a significantly higher prevalence of PIH.

The utilization of prenatal care (PNC) by the study population was found to be adequate for 42.5% and adequate plus for 32.4% but was inadequate for 12.8% and intermediate for another 12.3% of the participating women (Table 5-2). All the factors considered as covariates for the analyses were found to be significantly associated with utilization of prenatal care. The percentage of women with adequate prenatal care was higher among women with no history of IPV compared to women with history of IPV (48.7% vs. 38.0%), whereas the percentage with inadequate prenatal care utilization was higher for women with IPV history than without such

history (19.8% vs. 11.6%) (Table 5-1). Inadequate prenatal care utilization was prevalent among women less than 18 years of old, of racial/ethnic minority groups, less than high school educated, not married, and with household income less than $20,000 (Table 5-2). Percentage of women with inadequate prenatal care utilization was also high in women with no insurance or on Medicaid/public insurance, with higher number of stressor in life, with two or more previous live births, with history of previous preterm birth, and who were underweight and gained less than 11 lbs. during pregnancy. Bivariate logistic regression analyses showed statistically significant associations between IPV before and/or during pregnancy and PIH and also between PNC utilization and PIH (not shown in table). Women who utilized PNC inadequately were 1.04 times as likely and women with adequate plus PNC utilization were 2.18 times as likely to have PIH as women with adequate PNC utilization (Crude odds ratio (COR): 1.04, 95% confidence interval (CI): 1.01, 1.23 and COR: 2.18, 95% CI: 1.97, 2.42; respectively; not shown in table).

Income was found to be highly correlated with maternal age, education and marital status; and insurance status was found to be highly correlated with maternal education, marital status and income in the tests for multicollinearity; therefore income and insurance status were removed from the analysis. Further, stress during pregnancy were identified as a mediator on the pathway from IPV to PNC utilization and therefore was removed from that particular pathway analysis. The adjusted SEM model demonstrated a good fit with the observed data. The model fit statistics for the adjusted analysis were: $\chi 2$ (df= 8) =401.463, $p<0.0001$, RMSEA = 0.028 and CFI = 0.796. In the unadjusted analysis, the likelihood of higher order of prenatal care utilization was 14% less for women with history of IPV before and/or during pregnancy compared to women with no such history (Table 5-3) (‘Path a’ of indirect effect: Figure 5-3). This association remained significant but the strength attenuated after adjusting for maternal age,

race, education, marital status, prepregnancy smoking and alcohol use, parity, prepregnancy BMI, and pregnancy weight gain (adjusted odds ratio (AOR): 0.90, 95% CI: 0.89, 0.91, P=0.006)). Further, the odds of PIH was increased by 17% with one order increase in the Kotelchuck index of prenatal care utilization after controlling for the effect of IPV on PIH and other potential confounders in the adjusted analysis ('Path b' of indirect effect: Figure 5-3) (AOR: 1.17, 95% CI: 1.16, 1.18; p<0.0001) (Table 3).

The total, direct and indirect effects of IPV before and/or during pregnancy on PIH showing mediation by prenatal care utilization are presented in Table 5-4. The unadjusted path analyses revealed a significant total effect of IPV on PIH showing a 11% increased risk of PIH for women experiencing IPV before and/or during pregnancy (COR:1.11, 95% CI: 1.09, 1.12, p= 0.047), a significant direct effect after controlling for prenatal care utilization (COR:1.14, 95% CI: 1.12, 1.16, p= 0.036), and a significant indirect effect showing a 3% reduction in the odds of PIH through increased PNC utilization for women with history of IPV (COR: 0.97, 95% CI: 0.96, 0.98, p= 0.006). However, both the total and direct effects lost their statistical significances after adjusting for maternal race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, and pregnancy weight gain. In the adjusted model, the indirect effect of IPV before and/or during pregnancy on PIH shows that women with history of IPV have a 2% reduced odds of having PIH through increased utilization of PNC compared to women with no history of IPV around the time of pregnancy (AOR: 0.98, 95% CI: 0.97, 0.99, p= 0.045). The sensitivity analyses using PNC utilization as a continuous variable (# of PNC visits) showed similar total, direct, and indirect effects of IPV on PIH (Table 5-S1).

Discussion

Using structural equation modeling, the study found a statistically significant mediation effect of prenatal care utilization on the causal pathway between IPV around the time of pregnancy and PIH, showing a reduction in the odds of PIH through prenatal care utilization for the women experiencing IPV around the time of pregnancy; however the effect size was negligible. The study also revealed a significant association between IPV around the time of pregnancy and PNC utilization showing a reduction in utilization of PNC for women experiencing IPV around the time of pregnancy. The study further shows that PIH is significantly associated with increased utilization of prenatal care. However, the study was unable to find any significant total effect of IPV showing its influence on PIH after controlling for potential confounders. Further, the study did not find any significant direct influence of IPV on PIH after controlling the effect of PNC utilization and adjusting for potential confounders.

Results from this study that demonstrated a significant effect of IPV around the time of pregnancy on PNC utilization causing reduction in PNC utilization are consistent with the findings from previous studies and can be explained by the delayed entry into and under-attendance to PNC by the IPV victims due to controlling behavior by the abusive partner and lack of resources for the abused women. [37,183-185] For example, Jasinski (2004) found IPV to act as a barrier to adequate prenatal care. This study showed entry into prenatal care to be often delayed by the abused women and suggests that resources such as money or transportation may be withheld by the spouse or partner, making it difficult for women to attend scheduled appointments.[37]

However, findings from this study showing a significant association between increased PNC utilization and increased likelihood of PIH was unexpected and could be potentially

misleading and is in contrast with the findings of previous studies that suggested a decrease in the risk of PIH with adequate utilization of prenatal care.[177,178,186] The finding of the current study can be explained by the probability of increased utilization of prenatal care through frequent PNC visits due to being diagnosed with hypertension early in the pregnancy and therefore, being monitored closely. A study examining the clinical and psychosocial factors that differentiate adequate users from inadequate or excessive users of prenatal care found that women with hypertension, diabetes, preeclampsia, multiple gestation, and fetal abnormalities required additional prenatal care visits causing excessive use of prenatal care.[192] This finding is consistent with the results of the bivariate regression analysis in the current study showing a significant higher odds of PIH for the women with adequate plus prenatal care utilization compared to adequate prenatal care user. The data used for the current does not allow to establish directionality between utilization of prenatal care and the time of diagnosis of PIH. Therefore, it is hard to infer whether increased utilization of PNC led to increased risk of PIH or diagnosis of PIH led to increased utilization of PNC.

Further, results from this study showing significant indirect effect of IPV by reducing the risk PIH through reduced utilization of prenatal care could be misleading due to the possible misspecification of directionality between prenatal care utilization and development of PIH as PRAMS data is cross-sectional in nature. This misleading finding could also be due to the mediation ratio effect of mixture of negative coefficient estimate of association between IPV and PNC utilization and positive coefficient estimate of association between PNC utilization and PIH. The mediation ratio has been criticized for providing misleading estimates for structural equation models that include both positive and negative estimates.[193] Further, the insignificant findings of total and direct effects of IPV on PIH in the adjusted analyses can be explained by the

fact that IPV in the current study was measured as a binary variable and the effect of IPV on PIH could not be differentiated based on the frequency, nature, and/or intensity of IPV. This might have resulted in dilution of the effect of IPV on PIH, resulting in insignificant associations.

The current study has several strengths including being the first study, to the knowledge of the author, to explore the causal pathway between IPV around the time of pregnancy and PIH through the mediation effect of prenatal care utilization. The current study utilized a conceptual framework of social determinants of PIH to better understand the interrelationship between the reproductive and psychosocial factors at different levels of socio-ecologic model and their direct or indirect influence on PIH.[42] The study further utilized direct acyclic graph (DAG), an explicit visual representation of relationships between variables to identify the presence of potential confounding, moderation, or mediation beyond the traditional methods.[154] This study used a robust dataset with a large sample size and this national level data set provided results that are generalizable to the US women. Further, the use of SEM methodology allowed exploration of multiple pathways providing better understanding of the total, direct and indirect effect of IPV around the time of pregnancy on PIH.[189,190] Also, structural equation modeling analyses were performed in Mplus statistical software program allowing advanced modeling of binary outcome with categorical mediator variable for the current study.[191] Lastly, the main outcome of the study, PIH, was measured using a birth certificate variable collected directly from the medical record by a health care professional and therefore could be considered valid, reducing the risk of misclassification bias in the results.[45] Moreover, the measure used for main exposure variable, IPV around the time of pregnancy, was validated in other studies.[187,188] In addition, Kotelchuck index, a widely-used and valid measure of adequacy of PNC utilization,[176] was used to measure the utilization of PNC for the current study.

Despite these strengths, the current study has several limitations. Due to the cross-sectional nature of PRAMS data, causality cannot be inferred, however, due to the temporal sequence between prepregnancy IPV and utilization of PNC during pregnancy, temporality between IPV and PNC utilization can be assumed (Figure 5-4). But, the temporal sequence between PNC and PIH could not be established as the information on timing of PIH diagnosis for the participants were not available in the dataset and this might have resulted in misspecification of directionality for the SEM path analyses. Further, the mediation ratio might have provided misleading estimates because the mediation pathways in the current study included both positive and negative estimates.[193] Moreover, PRAMS data are self-reported and retrospective in nature and thereby may be subject to recall and social desirability biases by participants. Self-reporting of IPV, the exposure variable, might have introduced non-differential misclassification bias in the study causing under-estimated measures of associations, as IPV is known to be underreported.[194] Further, the intensity measure of IPV was not present in the dataset and therefore could not be analyzed. In addition, information on several factors that are strongly associated with PIH, such as history of chronic renal disease [44] and history of preeclampsia or gestational hypertension in a previous pregnancy,[44] were not available in the dataset and could not be assessed and therefore, might have caused residual confounding, causing overestimation or underestimation of associations. Further, PRAMS data did not allow the detection of women who might had underlying chronic hypertension that were undiagnosed because they presented late to prenatal care after 20 weeks and therefore, could not be excluded from the analyses.

Conclusion

IPV is a public health issue that can result in serious risks to maternal and infant health

outcomes. Similarly, PIH is associated with multiple adverse birth outcomes. The current study sought to explore the direct effect of IPV around the time of pregnancy and its indirect effect through mediation by prenatal care utilization on PIH. Even though, the current study found no significant total or direct effect of IPV around the time of pregnancy on PIH, it revealed a mediation effect of PNC utilization on the pathway between IPV and PIH. Women who experience IPV around the time of pregnancy have significantly less utilization of PNC and prenatal care utilization is significantly associated with PIH. It is important that health professionals focus on utilizing available screening tools to assess IPV in women of childbearing age during preconception period and in pregnant women during their first prenatal care visit and provide or refer women who screen positive to intervention services and ensure adequate prenatal care visits for pregnant IPV victims to reduce the additive risk of adverse pregnancy outcomes in these women. Further, early detection and proper intervention of hypertension during PNC care can prevent the progression of the disorder to further detrimental outcomes, such as preterm births and maternal mortality. Future research is necessary to further understand the directionality between PNC utilization and PIH and the true nature of the indirect effect of IPV on the risk of PIH through PNC utilization using longitudinal data. Future research can also look into the indirect effect of IPV on the PIH-related adverse outcomes through reduced utilization of PNC by the abused women.

Table 5-1. Distribution of intimate partner violence before and/or during pregnancy and prevalence of pregnancy induced hypertension according to characteristics of the study population; PRAMS 2009 -2015

Characteristics	Total (N= 64,618)	IPV before and/or during Pregnancy (N=2,650; 4.1%)	P-value (Rao-Scott Chi^2 Test)	PIH (N= 4,717; 7.3%)	P-value (Rao-Scott Chi^2 Test)
	%	%		Prevalence	
Socio-Demographic Factors					
Maternal Age			<.0001		0.0808
<18 years.	6.6	13.9		6.0	
18 -24 years	22.2	35.1		4.8	
25-29 years	30.9	28.3		5.2	
30- 34 years	26.5	15.3		5.5	
35+ years	13.8	7.4		5.8	
Race/Ethnicity			<.0001		<.0001
Non-Hispanic White	66.2	56.4		5.5	
Non-Hispanic Black	11.2	18.5		7.4	
Non-Hispanic Other	8.6	10.2		4.6	
Hispanic	14.0	14.9		4.0	
Maternal Education			<.0001		0.0027
Less than high School	13.3	21.0		4.9	
High School	24.1	37.9		5.4	
Some College	29.2	30.9		5.9	
Bachelor's degree or higher	33.5	10.2		4.8	
Marital Status			<.0001		0.0146
Not Married	36.2	73.1		5.7	
Married	63.8	26.9		5.1	
Household Income			<.0001		0.2583
Less than $20,000	29.4	66.7		4.8	
$20,000 to 34,999	20.2	18.7		6.1	
$35,000 to 49,999	11.7	6.9		4.8	
$50,000 or more	38.7	7.7		5.3	
Healthcare Access & Utilization Factors					
Insurance before Pregnancy			<.0001		0.5040
Private insurance	61.5	34.7		5.4	
Medicaid/Public insurance	17.4	37.2		5.2	
No insurance	21.1	28.1		5.1	
Prenatal Care Utilization			<.0001		<.0001
Inadequate	12.8	19.8		4.3	

Intermediate	12.3	13.6		3.3	
Adequate	42.5	38.0		4.1	
Adequate plus	32.4	28.6		8.6	
Residence			0.4550		0.9644
Rural	34.7	35.7		5.4	
Urban	65.3	64.3		5.4	
Substance Use/Health Behavioral Factors					
Smoked before Pregnancy			<.0001		0.0051
Yes	24.9	55.7		5.9	
No	75.1	44.3		5.1	
Alcohol Use before Pregnancy			<.0001		0.0046
Yes	64.6	73.4		5.6	
No	35.4	26.6		4.9	
Psychosocial Factors					
Number of Stressors during pregnancy			<.0001		0.3293
None	29.4	4.3		5.1	
1 to 2	24.2	6.8		5.1	
3 to 5	17.4	9.2		5.3	
6+	29.1	79.7		5.6	
Reproductive Factors and Pregnancy History					
Previous Live Births			0.0240		<.0001
None	40.3	41.0		7.0	
One	32.3	28.9		4.1	
Two or more	27.4	30.1		4.2	
Previous Preterm birth: Yes	3.3	3.4	0.7450	7.9	<.0001
No	96.7	96.6		5.2	
Prepregnancy BMI			0.0057		<.0001
Underweight (<18.5)	3.6	4.9		3.0	
Normal BMI (18.5 - 24.9)	48.1	44.3		3.4	
Overweight (25.0 -29.9)	25.0	24.2		5.4	
Obese (>=30.0)	23.3	26.6		9.2	
Prepregnancy Diabetes: Yes	1.2	1.4	0.3776	12.9	<.0001
No	98.8	98.6		5.2	
Pregnancy Weight gain			<.0001		<.0001
Less than 11 lbs.	5.9	8.6		5.4	
11 to 20 lbs.	15.4	15.4		5.1	
21 to 30 lbs.	28.8	24.0		4.1	
31 to 40 lbs.	27.5	25.3		4.9	
More than 40 lbs.	22.4	26.7		7.7	
Gestational Diabetes: Yes	5.1	4.4	0.2363	10.5	<.0001
No	94.9	95.6		5.0	

Abbreviations: IPV, Intimate partner violence; BMI, Prepregnancy Body Mass Index (kg/m^2)

Table 5-2. Prevalence of adequacy of utilization of prenatal care according to characteristics of the study population; PRAMS 2009-2015

Characteristics	Utilization of Prenatal Care				
	Inadequate (N=8,271; 12.8%)	**Intermediate (N=7,948; 12.3%)**	**Adequate (N=27,463; 42.5%)**	**Adequate Plus (N=20,936; 32.4%)**	**P-Value[a]**
	Prevalence				
Socio-Demographic Factors					
Maternal Age					<.0001
<18 years.	21.7	13.6	38.7	26.0	
18 -24 years	16.3	13.0	44.1	26.6	
25- 29 years	10.4	12.2	50.1	27.3	
30-34 years	8.8	12.1	51.6	27.5	
35+ years	9.7	12.3	49.1	28.9	
Race/Ethnicity					<.0001
Non-Hispanic White	9.0	11.9	50.6	28.5	
Non-Hispanic Black	19.5	14.3	40.5	25.7	
Non-Hispanic other	16.2	12.8	46.2	24.8	
Hispanic	17.5	13.0	44.8	24.7	
Maternal Education					<.0001
Less than high school	24.0	14.2	37.8	24.0	
High school	14.8	12.3	45.3	27.6	
Some college	10.2	12.2	49.0	28.6	
Bachelor's degree or higher	6.5	12.2	54.1	27.2	
Marital Status					<.0001
Not married	18.1	12.6	42.1	27.2	
Married	8.5	12.3	51.7	27.5	
Household Income					<.0001
Less than $20,000	17.1	11.0	43.2	28.7	
$20,000 to 34,999	10.0	11.1	50.2	28.7	
$35,000 to 49,999	7.6	7.9	56.0	28.5	
$50,000 or more	4.0	11.4	53.2	31.4	
Healthcare Access and Utilization Factors					
Insurance before Pregnancy					<.0001
Private insurance	7.4	12.2	52.3	28.1	
Medicaid/Public insurance	18.1	12.6	41.0	28.3	
No insurance	20.5	13.0	41.6	24.9	
Residence					0.0051
Rural	11.7	12.6	49.0	26.7	
Urban	10.7	11.7	50.6	27.0	

Substance Use/Health Behavioral factors					
Smoked before Pregnancy: Yes	11.0	12.4	49.8	26.8	<.0001
No	14.7	12.5	43.9	28.9	
Alcohol Use before Pregnancy: Yes	10.0	12.3	49.1	28.6	<.0001
No	15.4	12.7	46.9	25.0	
Psychosocial Factors					
Number of Stressors during pregnancy					<.0001
None	8.9	12.7	51.9	26.5	
1 to 2	10.9	12.0	49.8	27.3	
3 to 5	11.7	12.3	49.4	26.6	
6+	15.9	12.7	42.9	28.5	
Reproductive Factors and Pregnancy History					
Previous Live births					<.0001
None	10.5	11.9	49.1	28.5	
One	10.9	12.6	49.5	27.0	
Two or more	15.1	13.1	45.8	26.0	
Previous Preterm Birth					<.0001
Yes	14.1	11.1	34.2	40.6	
No	12.3	12.7	49.1	25.9	
Prepregnancy BMI					<.0001
Underweight (<18.5)	14.2	11.9	45.4	28.5	
Normal BMI (18.5 - 24.9)	11.8	13.1	51.0	24.1	
Overweight (25.0 -29.9)	12.1	12.9	47.9	27.1	
Obese (>=30.0)	12.6	11.6	45.0	30.8	
Prepregnancy Diabetes					<.0001
Yes	11.6	8.5	30.5	49.4	
No	11.9	12.5	48.5	27.1	
Pregnancy Weight gain					<.0001
Less than 11 lbs.	18.4	12.0	39.9	29.7	
11 to 20 lbs.	15.0	12.7	44.4	27.9	
21 to 30 lbs.	10.7	13.4	48.7	27.2	
31 to 40 lbs.	9.5	11.9	51.6	27.0	
More than 40 lbs.	10.3	12.3	50.3	27.1	
Gestational Diabetes					<.0001
Yes	11.0	8.6	36.7	43.7	
No	12.0	12.7	48.9	26.4	

Abbreviations: BMI, Prepregnancy Body Mass Index (kg/m^2)

[a] P-values are from Rao-Scott Chi-square tests

Table 5-3. Unstandardized estimates with standard error, odds ratio with 95% confidence interval, and p-values for regression pathways of the structural equation models for pregnancy induced hypertension

Dependent Variable	Independent Variable	Unadjusted β (SE)	COR (95% CI)	P-value	Adjusted β (SE)	AOR (95% CI)	P-value
PNC utilization	IPV	-0.15 (0.03)	0.86 (0.85, 0.87)	<0.0001	- 0.10 (0.03)	0.90 (0.89, 0.91)	0.006
	Maternal race	-0.10 (0.01)	0.90 (0.89, 0.91)	<0.0001	-0.05 (0.01)	0.95 (0.94, 0.96)	<0.0001
	Maternal education	0.10 (0.01)	1.11 (1.09, 1.13)	<0.0001	0.06 (0.01)	1.06 (1.05, 1.07)	<0.0001
	Prepregnancy smoking	-0.07 (0.02)	0.93 (0.92, 0.94)	0.006	-0.02 (0.02)	0.98 (0.98, 0.98)	0.184
	Prepregnancy alcohol use	0.14 (0.01)	1.15 (1.3, 1.17)	<0.0001	0.08 (0.01)	1.09 (1.08, 1.11)	<0.0001
	Gestational weight gain	0.09 (0.01)	1.10 (1.09, 1.12)	<0.0001	0.04 (0.01)	1.04 (1.03, 1.05)	<0.0001
PIH	IPV	0.13 (0.06)	1.14 (1.12, 1.16)	0.036	0.06 (0.07)	1.06 (1.00, 1.07)	0.360
	PNC utilization	0.17 (0.01)	1.19 (1.18, 1.20)	<0.0001	0.16 (0.01)	1.17 (1.16, 1.18)	<0.0001
	Maternal age	0.10 (0.00)	1.11 (1.11, 1.11)	0.312	-	-	-
	Maternal race	- 0.05 (0.01)	0.95 (0.95, 0.95)	<0.0001	- 0.03 (0.01)	0.97 (0.97, 0.97)	0.012
	Marital status	- 0.05 (0.02)	0.95 (0.94, 0.96)	0.020	- 0.01 (0.03)	0.99 (0.99, 0.99)	0.939
	Prepregnancy smoking	0.07 (0.02)	1.07 (1.06, 1.08)	0.007	- 0.04 (0.03)	0.96 0.96, 0.96)	0.190
	Prepregnancy alcohol use	0.06 (0.02)	1.06 (1.05, 1.07)	0.005	- 0.02 (0.02)	0.98 (0.98, 0.98)	0.496
	Parity	-0.14 (0.01)	0.87 (0.86, 0.88)	<0.0001	-0.17 (0.02)	0.84 (0.83, 0.85)	<0.0001
	Previous preterm birth	0.21 (0.05)	1.23 (1.21, 1.26)	<0.0001	0.36 (0.06)	1.43 (1.37, 1.50)	<0.0001
	Prepregnancy diabetes	0.47 (0.07)	1.60 (1.50, 1.71)	<0.0001	0.44 (0.08)	1.55 (1.45, 1.66)	<0.0001
	Prepregnancy BMI	0.23 (0.01)	1.26 (1.25, 1.27)	<0.0001	0.30 (0.02)	1.35 (1.33, 1.37)	<0.0001
	Gestational Diabetes	0.38 (0.03)	1.46 (1.43, 1.50)	<0.0001	0.29 (0.05)	1.34 (1.30, 1.37)	<0.0001
	Pregnancy weight gain	0.06 (0.01)	1.06 (1.06, 1.06)	<0.0001	0.10 (0.01)	1.11 (1.10, 1.12)	<0.0001

Abbreviations: β, unstandardized coefficient; SE, standard error; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; IPV, intimate partner violence; PIH, pregnancy induced hypertension; PNC, prenatal care utilization; BMI, body mass index

Table 5-4. Parameter estimates of total, direct and indirect effects of intimate partner violence on pregnancy induced hypertension

Parameter	Crude Model			Adjusted Model		
	Estimate (SE)	OR (95% CI)	P-value	Estimate (SE)	OR (95% CI)	P-value
Total effect of IPV on PIH	0.10 (0.06)	**1.11 (1.09, 1.12)**	0.047	0.02 (0.07)	1.02 (1.00, 1.02)[a]	0.723
Direct effect of IPV on PIH	0.13 (0.06)	**1.14 (1.12, 1.16)**	0.036	0.06 (0.07)	1.06 (1.00, 1.07)[b]	0.360
Indirect effect of IPV on PIH through mediation by PNC utilization	-0.03 (0.01)	**0.97 (0.96, 0.98)**	0.006	-0.02 (0.01)	**0.98 (0.97, 0.99)[c]**	0.045

Abbreviations: β, unstandardized coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; IPV, intimate partner violence; PIH, pregnancy induced hypertension; PNC, prenatal care utilization

[a] Adjusted for maternal age, race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, and pregnancy weight gain

[b] Adjusted for maternal age, race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, pregnancy weight gain, and adequacy of prenatal care utilization

[c] Adjusted for maternal age, race, education, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, pregnancy weight gain, and adequacy of prenatal care utilization

Supplemental Table for Aim 3

Table 5-S1. Sensitivity analysis using number of prenatal care visits as a continuous variable: Parameter estimates of total, direct and indirect effects of intimate partner violence on pregnancy induced hypertension

Parameter	Crude Model			Fully Adjusted Model		
	Estimate (SE)	OR (95% CI)	P-Value	Estimate (SE)	OR (95% CI)	P-Value
IPV → PNC (path a)	-0.70 (0.10)	*	<0.0001	- 0.61 (0.11)[a]	*	<0.0001
PNC → PIH (path b)	0.02 (0.00)	**1.02 (1.02, 1.02)**	<0.0001	0.01 (0.00)	**1.01 (1.01, 1.01)[b]**	<0.0001
Total Effect of IPV on PIH	0.10 (0.06)	**1.11 (1.09, 1.12)**	0.040	0.02 (0.07)	1.02 (1.00, 1.02)[c]	0.723
Direct effect of IPV on PIH	0.13 (0.06)	**1.14 (1.12, 1.16)**	0.034	0.06 (0.07)	1.06 (1.00, 1.07)[d]	0.468
Indirect effect of IPV on PIH through prenatal care	-0.02 (0.01)	**0.98 (0.97, 0.99)**	0.007	-0.01 (0.01)	**0.99 (0.98, 0.99)[e]**	0.0001

Abbreviations: β, unstandardized coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; IPV, intimate partner violence; PIH, pregnancy induced hypertension; PNC, prenatal care utilization

[a] Adjusted for maternal race, education, prepregnancy smoking and alcohol use, and pregnancy weight gain

[b] Adjusted for maternal age, race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, pregnancy weight gain, and IPV

[c] Adjusted for maternal age, race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, and pregnancy weight gain

[d] Adjusted for maternal age, race, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, pregnancy weight gain, and adequacy of prenatal care utilization

[e] Adjusted for maternal age, race, education, marital status, prepregnancy smoking and alcohol use, parity, previous preterm birth, prepregnancy BMI, prepregnancy diabetes, gestational diabetes, pregnancy weight gain, and adequacy of prenatal care utilization

* Odds ratio cannot be calculated from beta estimates of linear regression analysis

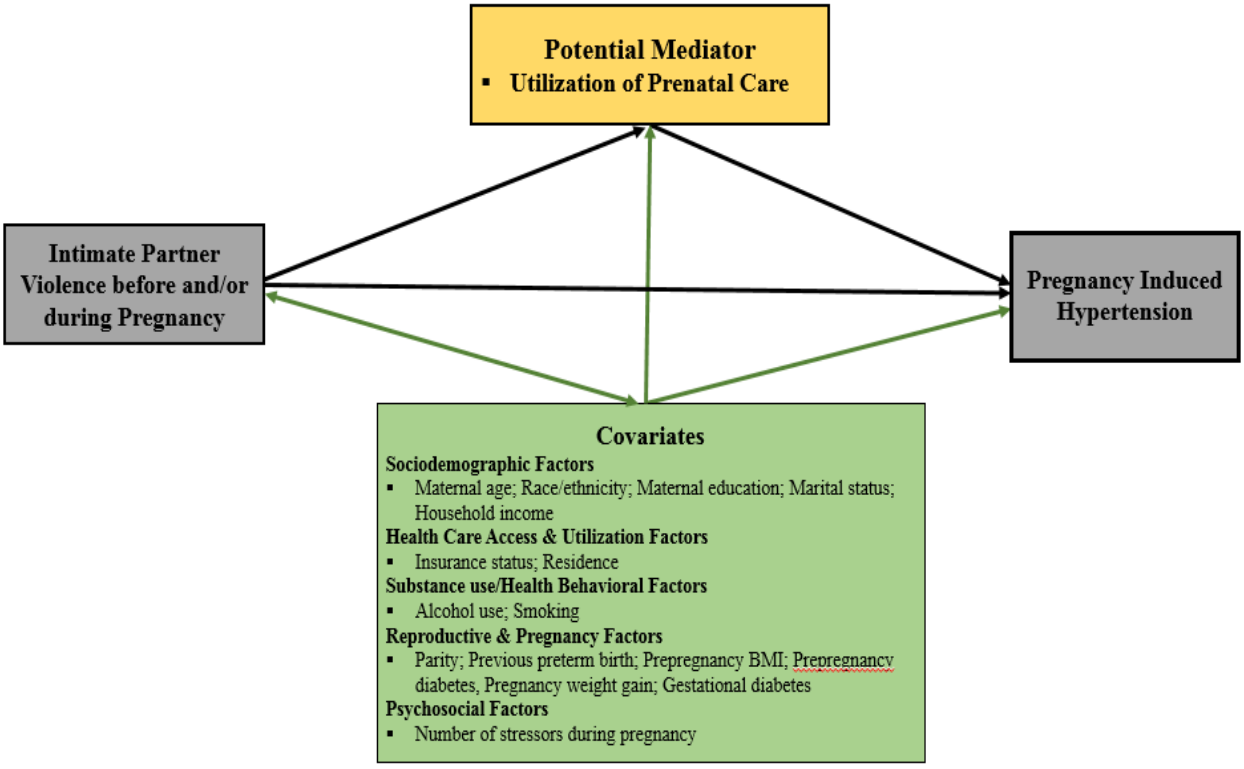

Figure 5-1. A hypothesized causal model of the association between intimate partner violence before and/or during pregnancy and pregnancy induced hypertension

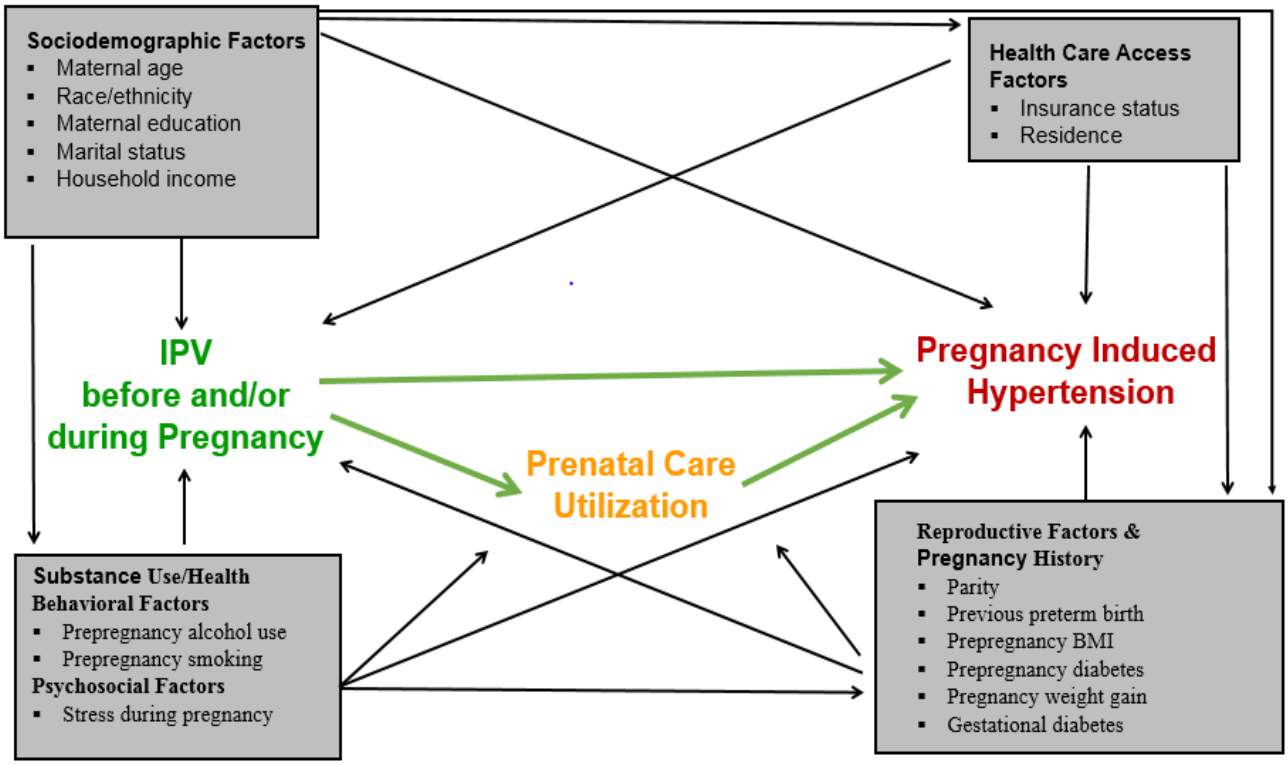

Figure 5-2. Directed Acyclic Graph (DAG) presenting potential mediation and confounding in the association between intimate partner violence before and/or during pregnancy and pregnancy induced hypertension

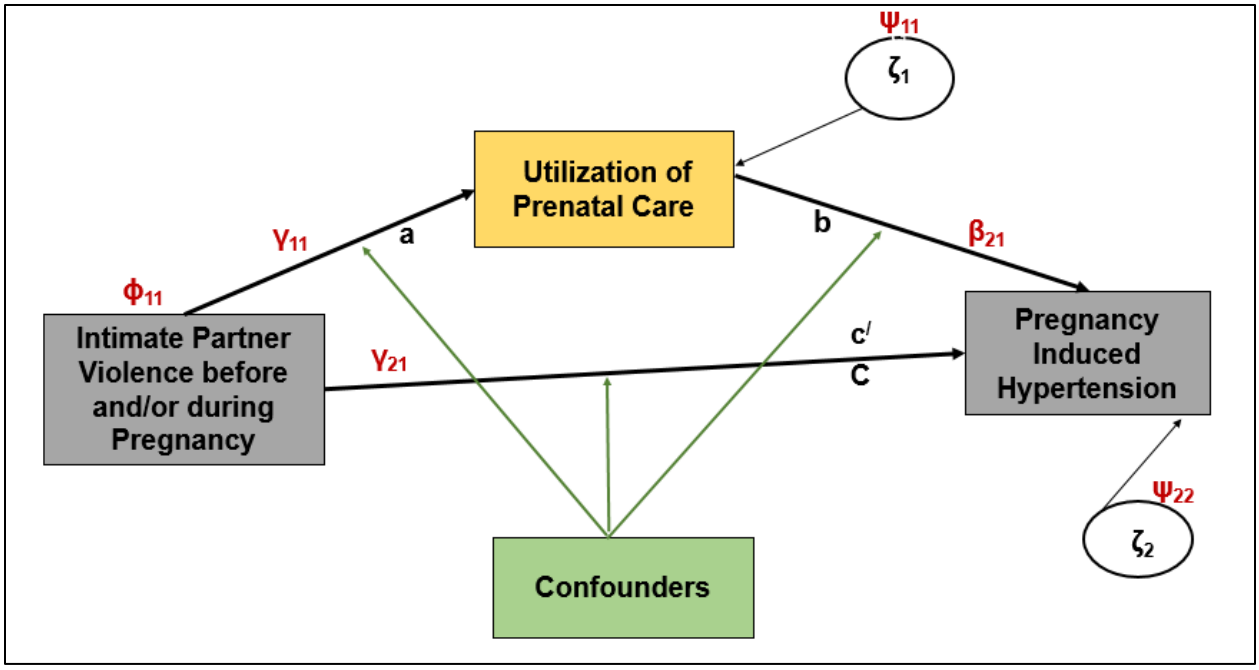

Figure 5-3. Statistical path mediation model for intimate partner violence before and/or during pregnancy and pregnancy induced hypertension

γ_{11}, γ_{21}, γ_{31}, β_{21} = Path coefficients; ϕ_{11} = Variance estimate for exogenous variable;

ψ_{11}, ψ_{22}, = Variance estimates for error terms

c' = Direct effect; C = Total effect; a*b = Indirect effect

ζ_1, ζ_2, = Error/disturbance terms

Confounders = Confounders on the mediation pathway through utilization of prenatal care

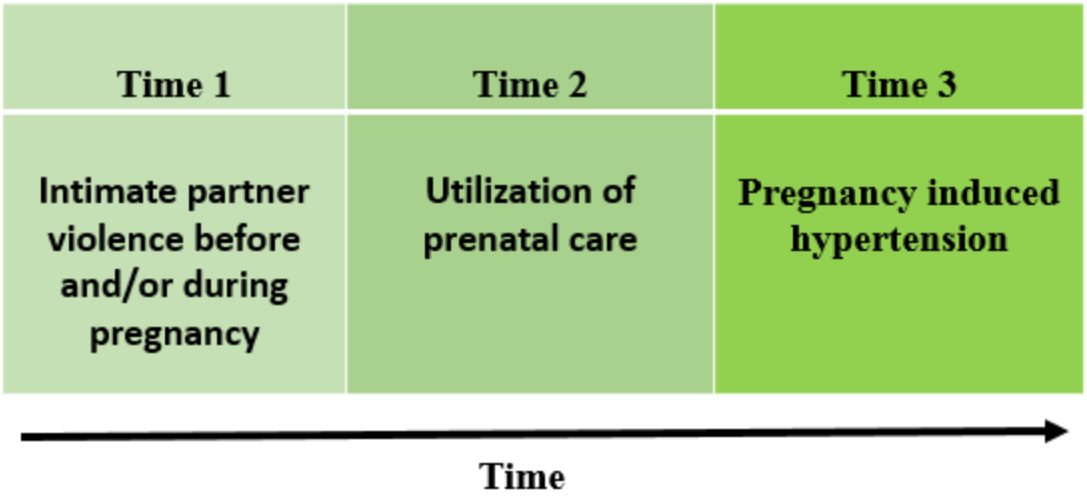

Figure 5-4. Temporal Sequence of Events Related to the Current Analysis

Chapter 6: Summary

Pregnancy induced hypertension (PIH, defined as 'the development of new hypertension during pregnancy after 20 weeks gestation')[1] is the leading cause of maternal mortality[3] and a major contributor to preterm birth and neonatal mortality.[2] In the United States, the incidence of PIH has significantly increased in the past two decades,[10,12] complicating up to 10% of all pregnancies;[3] however, the reasons for this rise are not well understood. PIH induced adverse outcomes can be prevented or ameliorated through early detection and interventions among high-risk population. The identification of important risk factors as well as description of role of these factors within the etiology of PIH is necessary to support comprehensive public health approaches to achieve optimal prenatal outcomes. Literature suggests that several modifiable psychosocial and health behavioral factors, such as physical inactivity, inadequate utilization of prenatal care, depression prior or during pregnancies, and intimate partner violence (IPV), may play significant roles in the development of PIH.[27,29,32,47,48,177,185] However, the interrelationships among these factors and their collective impact on PIH are not well studied. Better understanding of the interrelationship between these factors and their roles on PIH is important to fill in the knowledge gap, promote early detection of PIH and establish effective intervention programs targeting those amendable risk factors.

This dissertation was designed to better understand the interrelationship between some psychosocial and health behavioral factors and their role in the development of PIH. This research was grounded on the social determinants of health approach which suggests that PIH is the product of an interplay between multiple factors interacting at different levels (e.g., individual vs. neighborhood).[42] This dissertation aimed to examine the role of certain psychosocial and health behavioral factors including prepregnancy physical activity, prepregnancy depression, race/ethnicity, intimate partner violence before and/or during

pregnancy, and utilization of prenatal care services as risk or protective factors, mediators or moderators affecting PIH. Data for this dissertation came from the national level Pregnancy Risk Assessment Monitoring System (PRAMS) survey from years 2009 through 2015 and the research used Directed Acyclic Graphs (DAG) to identify potential covariates to include in the analyses. The analyses included hierarchical domain-adjusted multiple logistic regression modeling, multiple logistic regression modeling with stratification, and structural equation modeling. Statistical software SAS and Mplus were used for the analyses. The findings of this dissertation can be summarized as follows:

1) After adjusting for sociodemographic factors domain including maternal age, race/ethnicity, marital status and education, the study found that women who did exercise three days or more a week before pregnancy had a 10% lower odds of having PIH compared to women who did not exercise three days or more a week. However, the statistical significance disappeared after further adjustment of domains of substance use/health behavioral, psychological, and reproductive/pregnancy history factors.
2) Women who have had depression before pregnancy were found to be significantly more likely to have PIH compared to women who did not have prepregnancy depression in the adjusted analysis. Specifically, the odds of PIH was significantly higher among non-Hispanic White women experiencing prepregnancy depression.
3) Women who experience IPV before and/or during pregnancy are significantly less likely to utilize PNC adequately compared to women who do not have such experience. Moreover, increased utilization of prenatal care was significantly associated with increased odds of PIH. However, the current study found no statistically significant direct effect or total effect of IPV on PIH in the adjusted analyses.

The findings of this dissertation shed light on the interrelationships between different psychosocial and health behavioral factors and PIH.

Strengths

One of the major strengths of this study is utilization of a nationally representative sample of women with live births that allows inference to the general U.S. women population. Furthermore, it used a different approach by utilizing a conceptual framework to examine the interrelationship between multiple factors at different level of social determinants of PIH. Moreover, it utilized DAG to identify the potential mediating, moderating and confounding relationships between multiple reproductive and psychosocial factors and PIH. Also, the outcome measure, pregnancy induced hypertension, was based on information collected directly from the medical record using the facility worksheet; thereby increasing the validity of the results.[45] The use of innovative statistical technique for the analysis, such as SEM, allowed to present a more accurate estimate of mediation effect. The likelihood of technical analysis problems was limited because the model was recursive.[189] The Mplus software allowed advanced modeling of categorical variables for mediation analyses.[191] Furthermore, the results of this study points to screening during first prenatal visit for susceptible population at risk of developing PIH, based on certain psychosocial and health behavioral factors as an important measure for prevention of adverse consequences of PIH. It further proposes pre-conception and interconception counseling and guidance regarding prepregnancy physical activity, prepregnancy depression, and utilization of prenatal care as a measure of lowering the risk of and early intervention of PIH and thereby preventing further detrimental maternal and fetal health consequences.

Limitations

Despite its strengths, this study is not without limitations. First of all, PRAMS is a cross-sectional study and temporal relationships between exposures and outcome cannot be determined. Cross-sectional data is likely to produce biased estimate in mediation analysis because mediation is a causal process with directionality that happens over time. Misspecification of directionality could be present for variables measured in the cross-sectional data— which could lead to endogeneity. Directional specifications are not tested in SEM, rather, model fit is evaluated.[189] However, although data on exposure were not collected before the development of outcome, due to the temporal sequence between main exposures (intimate partner violence before pregnancy), mediators (utilization of prenatal care during pregnancy), and outcome (pregnancy induced hypertension, which is by definition at or after 20 week of gestation); directionality can be assumed (Figure 5-4). However, temporality between onset of prenatal care utilization and development of PIH could not be measured directly in the current analysis due to unavailability of necessary information, such as time of onset of PIH, in the dataset. Secondly, some potential confounding, mediating or moderating factors that could had affected estimates were not available in the dataset and could not be assessed. For example, information on antihypertensive treatment, antidepressant treatment prior to pregnancy, previous pregnancy induced hypertension, cardiovascular diseases, poverty, earlier history of intimate partner violence and child abuse, history of emotional and sexual abuse were not available in the dataset. These residual factors might have caused overestimation or underestimation of the actual measures in the current study. Furthermore, previous pregnancy induced hypertension is a major risk factor of pregnancy induced hypertension in the current pregnancy but it could not be assessed or excluded from the current analysis because of unavailability of information in the

dataset. Thirdly, IPV is usually underreported and might have resulted in non-differential misclassification causing a bias in the results towards the null.[194]

Public Health Implication

There are no reliable tools for early clinical diagnosis of pregnancy induced hypertension, nor effective treatment other than delivery of the fetus, highlighting the need to identify the modifiable risk factors. This study provided insight into the relationships between PIH and several psychosocial and health behavioral factors. Based on this insight, prepregnancy depression should be considered as part of a risk profile for PIH and screening of depression during antenatal care should be ensured focusing on certain racial/ethnic groups. Public health professionals and health care providers should be aware of the relationships between prepregnancy depression, race/ethnicity and PIH, and utilize the information in risk profiling, screening, early detection and intervention in women at risk of PIH. In addition, it is important that health professionals focus on utilizing available screening tools to assess IPV in women of childbearing age during preconception period and in pregnant women during their first prenatal care visit and provide or refer women who screen positive to intervention services and ensure adequate prenatal care visits for pregnant IPV victims to reduce the additive risk of adverse pregnancy outcomes in these women. Physical inactivity, increased prevalence of IPV, and inadequate utilization of prenatal care might be considered among the contributing factors that are associated with increased prevalence of gestational hypertension and preeclampsia in the US in past decades. Proper screening and intervention for IPV before and during pregnancy and assurance of adequate physical activity before pregnancy and prenatal care during pregnancy are essential to reduce the rate of adverse birth outcomes related to PIH and improve maternal and fetal health.

Knowledge gained from this dissertation have significant clinical and policy implications in addressing the roles of various psychosocial and health behavioral factors in the development of PIH. Early detection of at-risk population and early diagnosis of PIH based on these identified risk factors might help to trigger prompt medical management, and halt progression towards more detrimental maternal and neonatal outcomes such as pregnancy related maternal deaths, pre-term birth and neonatal mortality. Furthermore, knowledge gained from the proposed research will add important information in understanding the factors associated with PIH and guide future research.

Future Research

More studies are needed to investigate and confirm the interrelationship between prepregnancy physical activity, IPV, prenatal care utilization, and PIH. Specifically, clinical trial is needed to confirm the effect of pre-pregnancy physical activity on the risk of PIH. Further, longitudinal data is needed to understand the directionality between PNC utilization and onset of PIH and the true nature of the indirect effect of IPV on the risk of PIH through PNC utilization. Future research can also look into the indirect effect of IPV on the PIH-related adverse outcomes such as preterm births, low birthweight, and maternal mortality through reduced utilization of PNC by abused women.

Ethical Considerations

The study was exempted from review by the Institutional Review Board (IRB) at Virginia Commonwealth University as secondary data was utilized for analyses and there was no direct intervention or interaction with human subjects and no existing identifiable private information were accessed.

Chapter 7: References

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