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Maternal Smoking, Weight Status and Preecalmpsia and Eclampsia Risk Among Women Living in San Bernardino County

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MATERNAL SMOKING, WEIGHT STATUS AND PREECLAMPSIA AND ECLAMPSIA RISK AMONG WOMEN LIVING IN SAN BERNARDINO COUNTY

By

Fiona Bedelia Lewis

A Dissertation in Partial Fulfillment of the Requirements for the

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Each person whose signature appears below certifies that this dissertation, in his/her opinion, is adequate in the scope and quality as a dissertation for the degree of Doctor of Public Health.

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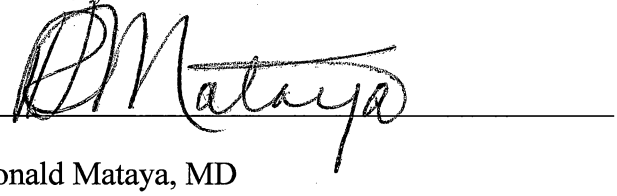

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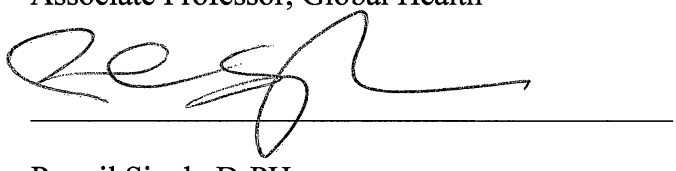

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ABSTRACT OF THE DISSERTATION

MATERNAL SMOKING, WEIGHT STATUS AND PREECLAMPSIA AND ECLAMPSIA RISK AMONG WOMEN LIVING IN SAN BERNARDINO COUNTY

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Doctor of Public Health in Preventive Care

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Preeclampsia is defined as pregnancy-induced hypertension affecting between 2% and 8% of pregnancies and accounting for about 10–15% of maternal deaths worldwide. Eclampsia is defined as the occurrence of one or more episodes of seizures in a pregnant woman related only to a preeclampsia diagnosis. Preeclampsia, if poorly managed, can progress to eclampsia resulting in injury and death to both mother and infant. The etiology of preeclampsia is not completely understood. Oxidative stress leading to abnormal placenta development and endothelial dysfunction are thought to be key components in the biological mechanism of preeclampsia.

Modifiable risk factors include maternal body weight and nutrition status, and preexisting medical conditions such as chronic hypertension and diabetes. Non-modifiable risk factors include maternal age, ethnicity, parity and genetics. African American women experience increased preeclampsia risk compared to women of other ethnicities.

The purpose of this cross-sectional study was to investigate the relationship between maternal smoking status, pre-pregnancy body mass index (BMI), Institute of Medicine (IOM) weight gain recommendations and preeclampsia, and eclampsia risk. Additionally to investigate how these relationships are affected by early prenatal care and participation in the Special Supplemental Nutrition Program for Women, Infants, and Children Program (WIC). San Bernardino County community health indicators highlight many socio-demographic challenges which may influence preeclampsia and eclampsia risk as well as other maternal and infant outcomes. The San Bernardino County Birth Cohort data from 2007-2008 were used in this study.

Frequencies, percentages, and multivariable logistic regression were used to investigate demographic characteristics of respondents and evaluate the relationship between maternal smoking, body mass index and preeclampsia and eclampsia risk. Statistical analyses were conducted using the Statistical Analysis Systems (SAS) software [version 9.3].

Results confirmed a strong association between maternal pre-pregnancy overweight/obesity and risk for preeclampsia and eclampsia. Respondents who were overweight or obese based on their pre-pregnancy BMI had increased odds of developing preeclampsia or eclampsia compared to those with normal pre-pregnancy BMI. Those gaining more than the IOM recommended weight gain also had increased odds of developing preeclampsia or eclampsia compared to those whose weight gain followed IOM recommendations. Finally, respondents who never smoked were noted to have a reduction in preeclampsia risk compared to those who smoked during pregnancy. No significant associations were noted between preeclampsia and eclampasia and smoking

cessation at recognition of pregnancy. Associations were also noted when accounting for the effects of WIC enrollment and early prenatal care.

In conclusion maternal overweight and obesity status remains a strong risk factor for preeclampsia and eclampsia. The relationship between maternal smoking and preeclampsia risk is an area which requires further exploration. Participation in the WIC program and early prenatal care are viable solutions to addressing maternal overweight or obesity status and nutritional deficiencies as well as smoking habits for the reduction of preeclampsia and eclampsia risk. Further investigation is warranted in exploring these options.

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CHAPTER 1 INTRODUCTION

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My deepest gratitude is extended to my mother, Lorna Elizabeth Leitch whose selfless sacrifices and continuous prayers have supported me throughout my doctoral journey and entire academic career. To my sister Keisha Nolita Baird, I appreciate your support and prayers. To my " village," the community of believers to which I belong: my New York and California families, Sisters Tuzale (Tracy-Ann Dawes, Ndinda Rebekah Ngewa, Aunamesha Henley, Pamela Mukaire and Obochi McKinney), Drs. Carlene Fider and Sherma Charlamange-Badal, the Sharpes and Mrs. Claudia Weekes.

Truly God has transformed me and gifted me for a lifetime of service for His glory!

CHAPTER 1

INTRODUCTION

A. Statement of the Problem

Preeclampsia is a hypertensive condition of pregnancy and is diagnosed when a woman with no history of hypertension develops hypertension and proteinuria after 20 weeks of gestation (Bell, 2010). Eclampsia is the onset of seizures related only to a preeclampsia diagnosis (Bell, 2010).

1. Maternal Morbidity, Mortality, and Preeclampsia Incidence Worldwide

Globally complications of pregnancy and childbirth are the leading causes of death among women of childbearing age, prompting the United Nations to include the improvement of maternal health as one of the Millennium Development Goals (Duley, 2009). Approximately 10% of women worldwide have hypertension during pregnancy, and preeclampsia affects approximately 2%-8% of pregnancies (Duley, 2009). The incidence of preeclampsia continues to increase worldwide, resulting in increased rates of death and injury among women of childbearing age (Eiland, Nzerue, & Faulkner, 2012).

2. Maternal Morbidity, Mortality and Preeclampsia Incidence in the United States

Annually approximately 240,000 women (1 in 10 pregnancies) in the United States experience hypertension during pregnancy (Mustafa, Ahmed, Gupta, & Venuto, 2012). According to the Centers for Disease Control and Prevention's summary (2013) on maternal mortality in the U.S., hypertensive disorders of pregnancy were responsible for 10.5% of maternal deaths between 2006 and 2008 in the U.S.

Hypertensive disorders of pregnancy were identified by Berg, Callaghan, Syverson and Henderson (2010) as one of the leading causes of maternal death in the U.S. between 1998 and 2005. Increases in rates of preeclampsia and gestational hypertension in the U. S. were noted between 1984 and 2004 (Wallis, Saftlas, Hsia, & Atrash, 2008).

3. Maternal Morbidity, Mortality, and Preeclampsia Incidence in California

According to the San Bernardino County Community Indicators Report (2011), California maternal death rates have fluctuated over the past 30 years but rose from 11 deaths per 100,000 live births in 2007 to 14 deaths per 100,000 live births in 2008. In 2008 non-Hispanic African American women had higher rates of maternal death compared to women of other ethnic groups nationally and in the state of California (Community Foundation, 2011). Another trend is the increase in maternal morbidity due to complications of pregnancy which includes (a) gestational diabetes, (b) preeclampsia, and (c) hemorrhage (California Department of Public Health [CDPH], 2011).

The California Pregnancy Associated Mortality Review (CA-PMR) Committee was created in 2004 by the California Department of Public Health's Maternal, Child and Adolescent Health Division for the purpose of investigating the increase in maternal mortality and ethnic disparities in this area (California Department of Public Health, 2011). The CA-PMR Committee found that between 2002 and 2004 preeclampsia was among the top six leading causes of pregnancy related maternal mortality (CDPH, 2011). Hispanic women were more likely to die from preeclampsia or eclampsia than women from other ethnic groups (CDPH, 2011).

4. *Adverse Maternal and Infant Outcomes Associated with Preeclampsia*

Preeclampsia affects multiple maternal organs including the liver, brain, and kidneys (Duley, 2009; Mustafa et al., 2012). Maternal outcomes include (a) HELLP Syndrome, which is characterized by hemolysis, elevated liver enzymes, and low platelets; (b) pulmonary edema, (c) hemorrhagic and ischemic strokes; (d) renal failure and hepatic failure, and death (Mustafa et al., 2012). The consequences of preeclampsia extend beyond the events surrounding pregnancy and delivery, since women with a history of diabetes mellitus or preeclampsia in pregnancy are at increased risk for developing cardiovascular diseases in the future (Kvehaugen, Andersen, & Staff, 2010). Postpartum quality of life is also affected by the experience of preeclampsia during pregnancy. Quality of life scores were noted to be lower at 6 and 12 weeks postpartum in women experiencing mild preeclampsia during pregnancy compared to those with pregnancies uncomplicated by preeclampsia (Hoedjes et al., 2011). In addition, women experiencing severe preeclampsia had lower quality of life measures than those with mild preeclampsia (Hoedjes et al., 2011).

Consequences of preeclampsia to the fetus include impaired fetal growth, premature birth, and death (Levine et al., 2004). Short gestation and low birth weight were among the top five leading causes of infant mortality in the U.S. in 2007 (Mathews & MacDorman, 2011). Short gestation due to complications of pregnancy such as preeclampsia and eclampsia interferes with the fetus's ability to grow and develop normally. Comparing neonates who were delivered early due to preeclampsia to those who were delivered early for other reasons, the former were more likely to be small for gestational age and experience respiratory distress syndrome than those delivered early

for other reasons (Jelin et al., 2010). Low birth weight infants born to mothers with preeclampsia experienced adverse outcomes beyond the immediate neonatal phase. These babies are at increased risk for stroke, heart disease, and metabolic syndrome later in life (Uzan, Carbonnel, Piconne, Asmar, & Ayoubi, 2011).

5. Economic Burden of Preeclampsia and Eclampsia

Besides morbidity and mortality, the adverse maternal and infant outcomes associated with preeclampsia and eclampsia increase healthcare costs further contributing to the economic burden associated with healthcare. Pregnancies complicated by hypertension were among the maternal conditions which increased between 1997 and 2009 in the U.S. (Wier et al., 2011). In 2009, vaginal pregnancies complicated by hypertensive conditions including preeclampsia and eclampsia occurred at a rate of 77 per 1,000 stays, while cesarean section deliveries complicated by hypertensive conditions were 137 per 1,000 stays in the U.S. (Stranges, Wier, & Elixhauser, 2012). Cesarean deliveries and vaginal deliveries with complications resulted in the longest and most expensive hospital costs (Stranges et al., 2012).

6. Non Modifiable Risk Factors

Non-modifiable maternal associated risk factors for preeclampsia include (a) age greater than 35 years, (b) African American, (c) multiple pregnancy, (d) insulin dependent diabetes, (e) parity, and (f) family history of preeclampsia (Duckitt & Harrington, 2005; Eiland et al., 2012).

7. Modifiable Risk Factors

Modifiable maternal associated preeclampsia risk factors include (a) overweight and obesity measured by the body mass index (BMI), (b) nutrition status, (c)

previous preeclampsia, (d) time between pregnancies, and (e) preexisting medical conditions such as chronic hypertension, diabetes mellitus, and kidney and autoimmune disease (Duckitt & Harrington, 2005; Eiland et al., 2012).

8. Nutrition Status and Preeclampsia Risk

Calcium and vitamin D supplementation appear to be promising in preventing preeclampsia in women experiencing these nutrient deficiencies (Shand, Nassar, Von Dadelszen, Innis, & Green, 2010; Xu, Shatenstein, Luo, Wei, & Fraser, 2009). A strategy most often used to improve the nutritional status of pregnant women is nutrition education and counseling which has been proven to be effective in improving gestational weight gain, reducing anemia, increasing birth weight and reducing preterm births (Girard & Olude, 2012). Girard and Olude (2012) indicated that increased effectiveness of nutrition education and counseling was noted when mothers were provided with food or supplements.

The purpose of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is to ensure that low income pregnant, breastfeeding, postpartum women; infants and children up to age five are adequately nourished (Lazariu-Bauer, Stratton, Pruzek, & Woelfel, 2004). Besides providing supplemental foods this national program provides nutrition education as well as referrals for social and medical services (Lazariu-Bauer et al., 2004). The goals for prenatal care include the prevention of deficiencies in iron, calcium, vitamins A and C, as well as protein and calories (Lazariu-Bauer et al., 2004). The WIC program makes available the opportunity for mothers to avoid nutrient deficiencies by providing increased access to nutrient rich foods. Consumption of foods offered in WIC food packages may help to improve nutrition

status thus preventing nutrient deficiencies linked to increased preeclampsia risk. The nutrient rich foods provided may also ameliorate the effects of the oxidative stress component associated with preeclampsia (Xu et al., 2009).

9. Preconception and Prenatal Care Preeclampsia Risk

Preconception care can be described as care given to ensure that a woman is healthy prior to becoming pregnant, during and between pregnancies (Posner, Johnson, Parker, Atrash, & Biermann, 2006). The Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry's Select Panel on Preconception Care indicated that the purpose of preconception care should be to identify and modify maternal risk factors (biomedical, behavioral, and social) which may otherwise result, adversely affect pregnancy outcomes, through prevention and management (Posner et al., 2006).

The importance of prenatal care on birth outcomes was demonstrated by the Omaha Healthy Start program, a community based prenatal care initiative. This program was created in 2001 to provide coordinated case management for improving perinatal health disparities in Douglas, Nebraska (Cramer, Chen, Roberts, & Clute, 2007). Services included case management, home visits, transportation, and screening, referrals, and health education (Cramer, Chen, Roberts, & Clute, 2007). Program administrators noted improvements in birth outcomes: (a) low birth weight, (b) infant mortality, and (c) hospital related cost savings over a 2 year period (Cramer et al., 2007).

Prenatal care is also important in the prevention of adverse pregnancy outcomes specifically relating to preeclampsia and eclampsia. Compared to women receiving any level of prenatal care, those receiving no prenatal care are seven times more likely to die

from complications of preeclampsia or eclampsia (MacKay, Berg, & Atrash, 2001). The reduction in risk was found to be greater in Caucasian women compared to African American women (MacKay et al., 2001).

10. Maternal Body Mass Index and Preeclampsia

A common measure of weight status for adults is the Body Mass Index (BMI). According to the Centers for Disease Control and Prevention, a person's height and weight can be used to calculate their BMI and used as an indirect measure of body fat which correlates with direct measures of body fat such as bioelectric impedance and under water weighing (2011). There are 4 weight categories: (a) underweight (< 18.5kgm/m^2), (b) normal (18.5kg/m^2-24.9kg/m^2), (c) overweight (25.0-29.9kg/m^2), and (d) obese (> 30.0kg/m^2) (CDC, 2011).

Over the past few decades there has been an increase in obesity prevalence in the U.S. (Ogden, Carroll, Kit, & Flegal, 2012). Between 2001 and 2011 there has been an increase in obesity among women of childbearing age in the U.S. (March of Dimes, 2012). Obese pregnant women (BMI >30kg/m^2) experience 2- 3 times the odds of developing preeclampsia and the results may be increased risk of preterm births (Zera, McGirr, & Oken, 2011). Excess body fat, especially central adiposity, is associated with increases in markers of chronic inflammation (Festa et al., 2001), which results in increased oxidative stress and consequently, increased preeclampsia risk.

11. Cigarette Smoking and Preeclampsia

In 2008, thirteen percent of women in the U.S. reported smoking during the last three months of pregnancy (CDC, 2012). Among the women who smoked three months before pregnancy, 45% quit during pregnancy, but sadly, approximately 50%

begin smoking within six months of delivery (CDC, 2012). Smoking during and after pregnancy increases infant mortality and morbidity (CDC, 2012).

Consistent findings point to a protective effect of cigarette smoking against preeclampsia (Ness, Zhang, Bass, & Klebanoff, 2008). The observed protection of cigarette smoking against preeclampsia risk appears to be related to the products of combustion such as carbon monoxide rather than the nicotine, which is also found in smokeless tobacco (Wikstrom, Stephansson, & Cnattingius, 2010). Wikstrom and colleagues (2010) noted that among cigarette smokers, heavy smokers (>9 cigarettes per day) experienced a greater reduction in preeclampsia and gestational hypertension risk compared to light smokers (1 to 9 cigarettes per day). This dose dependent relationship was weaker among overweight and obese women (Ness et al., 2008).

12. San Bernardino County Background and Community Health Indicators

a. Background San Bernardino County is the 5th largest county in California based on population, with approximately two million residents (Community Foundation, 2011). The median age of its residents is 32 years old, with 30% of residents under 18 years old (Community Foundation, 2011). The ethnic make-up of San Bernardino is as follows: (a) 49% Hispanic, (b) 33% Caucasian, (c) 8% Black and African American, (d) 6% Asian or Pacific Islander, (e) 0.4% American Indian and Alaska Native, (f) 2% multiple races (two or more races) (Community Foundation, 2011).

Between 2002 and 2012 San Bernardino County's unemployment rates were higher than the national unemployment rate, resulting in an increase in poverty and the number of residents without health insurance (Community Foundation, 2011). According

to the 2012 report, enrollment in public assistance programs such as (a) Food Stamps, (b) CalWORKs, and (c) Medi-Cal increased during 2011. Food Stamps provide vouchers to low income families to assist with food purchases, CalWORKs provides cash benefits for children in low income families and Medi-Cal allows low income families to have access to health care (San Bernardino County Community Indicators Report, 2012).

b. Community Health Indicators The San Bernardino County Community Indicators Report for 2012 showed gains in several areas as well as opportunities for improvement regarding the health of its residents. Prematurity/low birth weight and maternal complications of pregnancy were among the top five leading causes of death in infants under 1 year old (San Bernardino County Community Indicators Report, 2012). The 2012 San Bernardino County Community Indicators Report also indicated that early prenatal care rate was 81.7%, a rate that is in absolute terms 3.8% higher than Healthy People 2020 goal of 77.9%., but still the lowest among comparable counties in California. In 2010, the use of early prenatal care services was highest among Whites, Asians, and Hispanics (San Bernardino County Community Indicators Report, 2012). However, births were highest among Hispanics, followed by Whites then African Americans, indicating that although African American women ranked third according to birth rate they lagged behind other ethnic groups seeking early prenatal care (San Bernardino County Community Indicators Report, 2012).

Additionally the 2012 San Bernardino County Community Indicators report revealed that the County had adult overweight and obesity rates which were higher than in neighboring counties and still rising: the second highest diabetes rates in California

(10.6%) after Los Angeles County (10.9%). The age adjusted heart disease mortality rate did not meet Healthy People 2020 goals.

Tobacco use including cigarette smoking among San Bernardino's adult residents decreased from 16.9% in 2007 to 15% in 2009 (Healthy San Bernardino County, 2012). In 2009 rates for tobacco use were higher among males and residents between the age of 25 and 44 years old (Healthy San Bernardino County, 2012). Among ethnic groups tobacco use was as follows: (a) Asian (35%), (b) American Indian/Native American (20.6%), (c) White (17.6%), (d) African Americans (15.2%), and (e) Latino (8.7%) (Healthy San Bernardino County, 2012). It is not clear how these patterns of tobacco use may affect preeclampsia risk among women living in San Bernardino County.

13. San Bernardino County Epidemiological Birth Outcome Studies

A study similar to the proposed study explored the association between race/ethnicity and other maternal factors to adverse birth outcomes (Nanyonjo, Montgomery, Modeste, & Fujimoto, 2008). Researchers utilized data from the California Department Health Services Office of Vital Statistics birth cohort for 1999-2001 (n=86,736). Compared to Hispanic and White women, Black women had higher infant mortality rates and babies with lower mean birth weights (Nanyonjo et al., 2008). Among Black women (a) education, (c) maternal age, (d) insurance, and (e) length of gestation were predictors of moderate (1,500-2,499g) and low birth weight (<1,500g) infants (Nanyonjo et al., 2008).

B. Purpose of the Study

Preeclampsia and eclampsia risk among women living in San Bernardino County may be affected by some of the community health indicators mentioned, specifically (a)

obesity, (b) tobacco use, (c) ethnic disparities in utilization of prenatal care, and (d) lack of health insurance due to unemployment.

The purpose of this study was to investigate the relationship between preeclampsia and eclampsia risk, maternal weight status per pre-pregnancy BMI and IOM weight gain recommendations and smoking status. Additionally the effects of early prenatal care and enrollment in the WIC program on the aforementioned relationships were explored.

Early detection/screening, management through medication and preterm delivery appear to be the current approach in clinical practice to ameliorating the effects preeclampsia and eclampsia. However, these methods are focused on addressing the conditions after they have emerged. The results of this study may help to provide additional, evidenced-based support for preeclampsia risk reduction through modification of maternal factors.

C. Research Questions

From the 2007-2008 San Bernardino County Cohort Birth Records:

1. What is the relationship between maternal pre-pregnancy BMI and preeclampsia and eclampsia risk?
2. What is the relationship between Institute of Medicine (IOM) weight gain recommendations and preeclampsia and eclampsia risk?
3. What is the relationship between maternal smoking status and preeclampsia and eclampsia risk?

D. Mechanisms

1. The Models of Preeclampsia

Several maternal factors have been identified as risk factors for preeclampsia; however, no single theory exists which explains the etiology of the condition, nor is there a complete understanding of its pathophysiology (Bell, 2010; Odegard, Vatten, Nilsen, Salvesen, & Austgulen, 2000). Oxidative stress and inflammation appears to be one of the key components in several mechanisms proposed to explain the occurrence of the preeclampsia. During normal pregnancies immune adaptations occur in favor of T-helper 2 cell (Th-2) immune responses instead of T-helper 1 cell (Th-1) responses which may harm the fetus (Eiland et al., 2012). In preeclamptic pregnancies there appears to be an increase in systematic inflammation due to increase T-helper 1 dominated immune responses (Eiland et al., 2012). T-helper cells are cytokines involved in the body's immune response and function in the following way:

> Th1 cells drive the type-1 pathway ("cellular immunity") to fight viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. Th2 cells drive the type-2 pathway ("humoral immunity") and up-regulate antibody production to fight extracellular organisms; type 2 dominance is credited with tolerance of xenografts and of the fetus during pregnancy. Over activation of either pattern can cause disease, and either pathway can down-regulate the other. (Kidd, 2003, p. 223).

Inflammation is the result of the body's defense against harmful stimuli (Monteiro & Azevedo, 2010). Chronic inflammation results when the body is unable to destroy the harmful stimuli which triggered the inflammatory response, or cells involved in the inflammation process do not die and continue to release inflammatory substances (Monteiro & Azevedo, 2010). As a result, several detrimental changes occur in the body: (a) damage to tissues, (b) oxidative stress, (c) growth of new blood vessels, and (d) the

development of fibrous bands which cause thickening and hardening of tissues (Libby, 2007). This inflammatory process has been associated with chronic conditions such as metabolic syndrome, obesity, and atherosclerosis (Libby, 2007; Monteiro & Azevedo, 2010). Biomarkers of chronic inflammation/oxidative stress include C-reactive Protein (CRP), chemokines and cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), (Monteiro & Azevedo, 2010). TNF-α is associated with endothelial dysfunction and is involved in lipid metabolism, clotting and insulin resistance (Founds et al., 2008). Elevated TNF-α levels were noted in pregnant preeclamptic mothers regardless of weight status (Founds et al., 2008).

In 2008, Azim, Tsering, Neena and Pasha proposed a model for the development of preeclampsia which involves the interaction of four factors: (a) immune maladaptation, (b) placenta ischemia, (c) oxidative stress, and (d) genetic susceptibility. Figure 1 depicts the interaction of these four components.

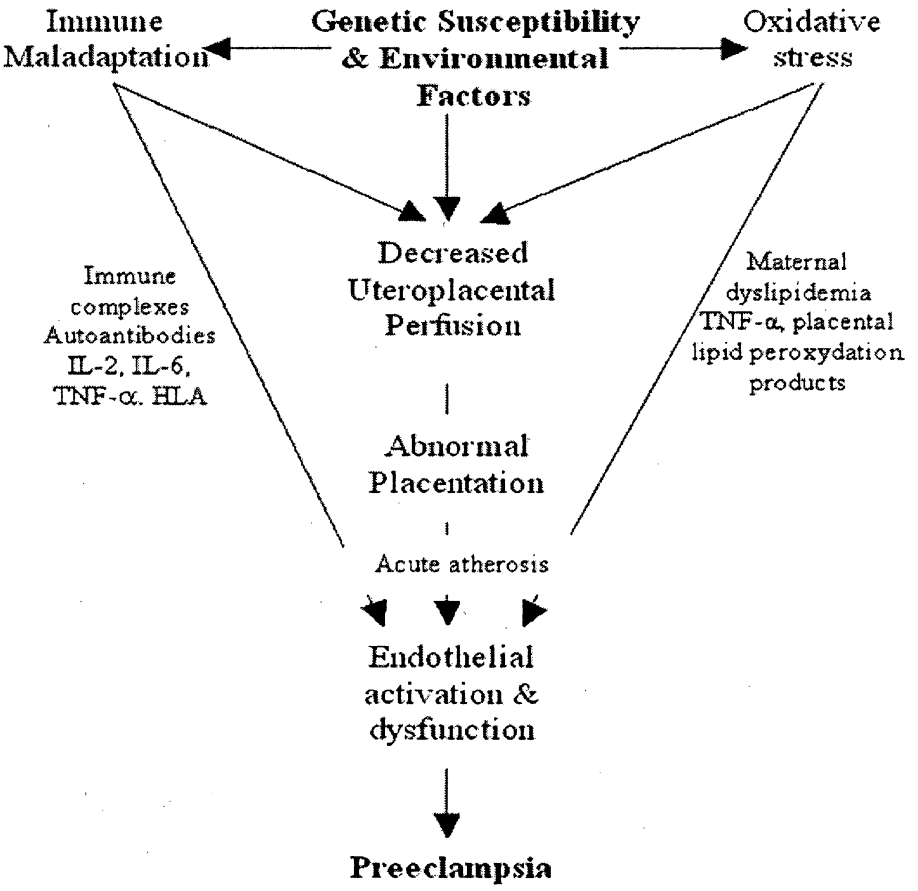

Figure 1.1 Interaction between factors (immune, genetic, environment, oxidative stress, and endothelial dysfunction) and their relationship to preeclampsia occurrence (Azim et al., 2008).

Gene-environment interactions result in the variations in expression of several genes, including those associated with the rennin-angiotensin system and nitric oxide synthase (Azim et al., 2008). The renin-angiotensin system is involved in the regulation of blood pressure, and nitric oxide is a vasodilator (Azim et al., 2008). During normal pregnancy the balance between vasoconstriction and vasodilation is achieved when bradykinin causes the release of nitric oxide, prostacyclin and reactive oxygen species/free radicals (Azim et al., 2008). The increased release of reactive oxygen species helps to modulate the AT1(angiotensin) receptor resulting in a decreased reaction

to angiotensin II (Azim et al., 2008). In the case of preeclampsia the AT1 receptor is less responsive due to its heterodimer formation with the B1 receptor (bradykinin), setting the stage for the formation of peroxynitrite, a powerful vasoconstrictor (Azim et al., 2008).

The combination of (a) genetic susceptibility and environment factors, (b) oxidative stress, and (c) immune maladaptation lead to numerous changes during pregnancy. These changes include structural abnormalities in the development of the placenta, and decreased flow of fluids through the placenta (decreased placental perfusion) which leads to thickening and hardening of cells lining the placenta (endothelial dysfunction) resulting in preeclampsia (Azim et al., 2008).

Azim and colleagues (2008) also elaborated on the relationship between what they refer to as environmental factors, such as calcium deficiency, high fat intake, psychological stress, and chronic infections, and the occurrence of preeclampsia in Figure 2. These environmental factors result in dyslipidemia (increases in LDL, oxidized LDL, triglyceride levels, and cholesterol) and increased inflammatory markers (TNF-α, IL-6, and CRP) (Azim et al., 2008). Dyslipidemia and increased inflammatory markers result in the production of peroxynitrite, leading to the inflammation and damage to blood vessel lining, and ultimately, preeclampsia (Azim et al., 2008).

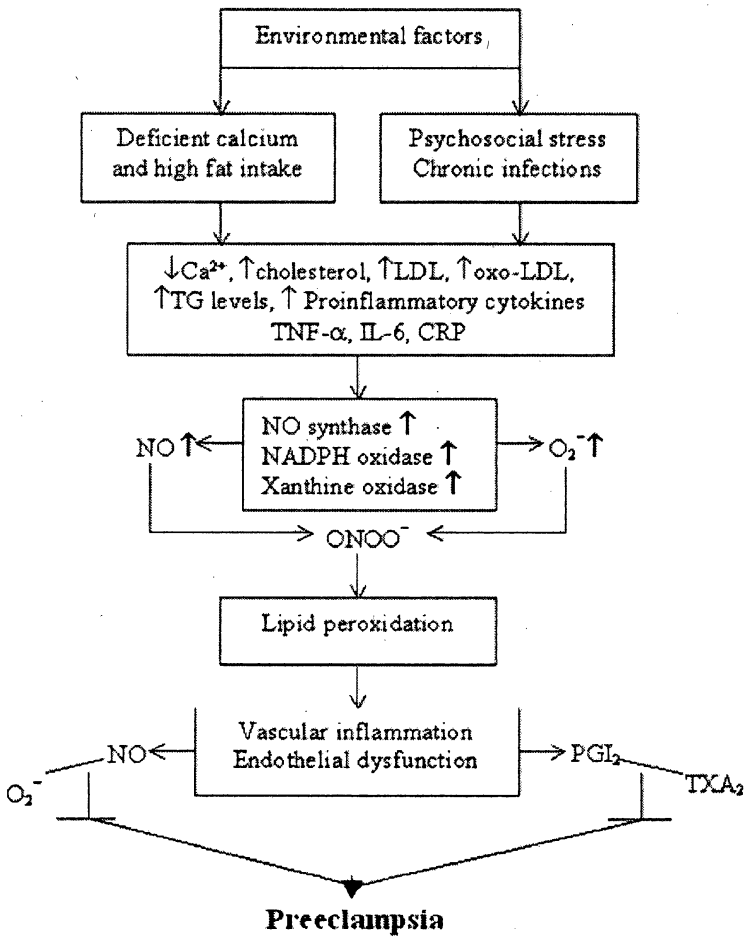

Figure 1.2 Contribution of environmental factors (calcium deficiency, high fat intake, psychological stress, chronic infections) in the pathophysiology of preeclampsia (Azim et al., 2008).

Xu and colleagues (2009) developed a model similar to Azim and colleagues (2008). However, Xu and colleagues (2009) added several additional factors: (a) socio-demographic (ethnicity, health care, social context), (b) maternal lifestyle (c) maternal nutrition status, (d) maternal medical history, (e) paternal factors, and (f) environmental factors. Figure 3 represents the hypothesized mechanism for this proposed research study elucidating the interactions between maternal variables and preeclampsia risk.

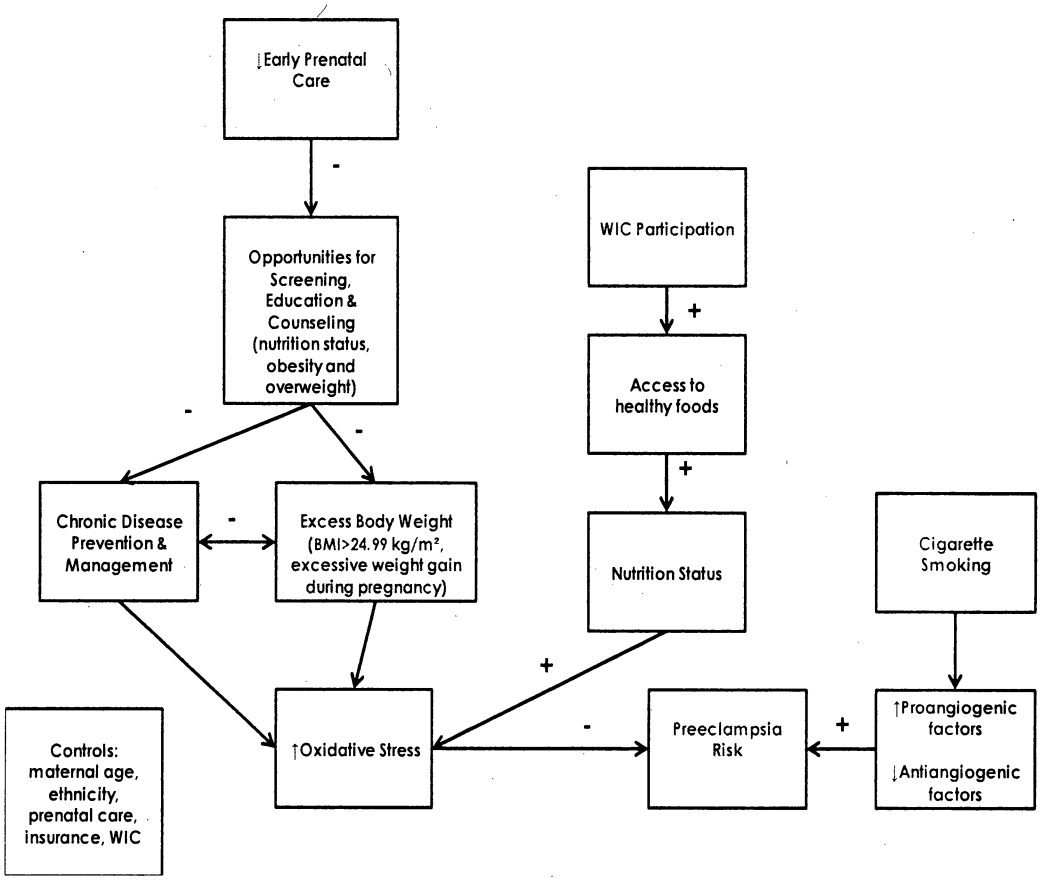

Figure 1.3 Schematic representation of the proposed relationship between maternal factors: Excess body weight, cigarette smoking, WIC participation, and prenatal care.

2. *Hypothesized Mechanism*

a. BMI and Excessive Gestational Weight Gain Preeclampsia risk has been noted to increase with gestational weight gain and increasing BMI (Langford, Joshu, Chang, Myles, & Leet, 2011; Mbah et al., 2010; Park et al., 2011). Excess adipose tissue due to weight gain creates a state of chronic inflammation due to increased circulation of inflammatory agents (Festa et al., 2001). There is also interplay between excess adipose and chronic disease, especially visceral fat, which is associated with insulin resistance due to increased interleukin-1 (IL-1) and pro-inflammatory cytokine, activity thus

providing a link to diabetes, (Tack, Stienstra, Joosten, & Netea, 2012). Biomarkers of inflammation, fibrinogen and C-reactive protein (CRP), were noted to be associated with various measures of body fat in diabetic and non-diabetic subjects who were non-Hispanic White, African American or Mexican American subjects (Festa et al., 2001). These findings were stronger for women (Festa et al., 2001). Figure 4 depicts a pictorial representation of the relationship between increased adipose tissue due to maternal factors and several chronic conditions, including pregnancy hypertensive disorders (Callaway, O'Callaghan, & McIntyre, 2009).

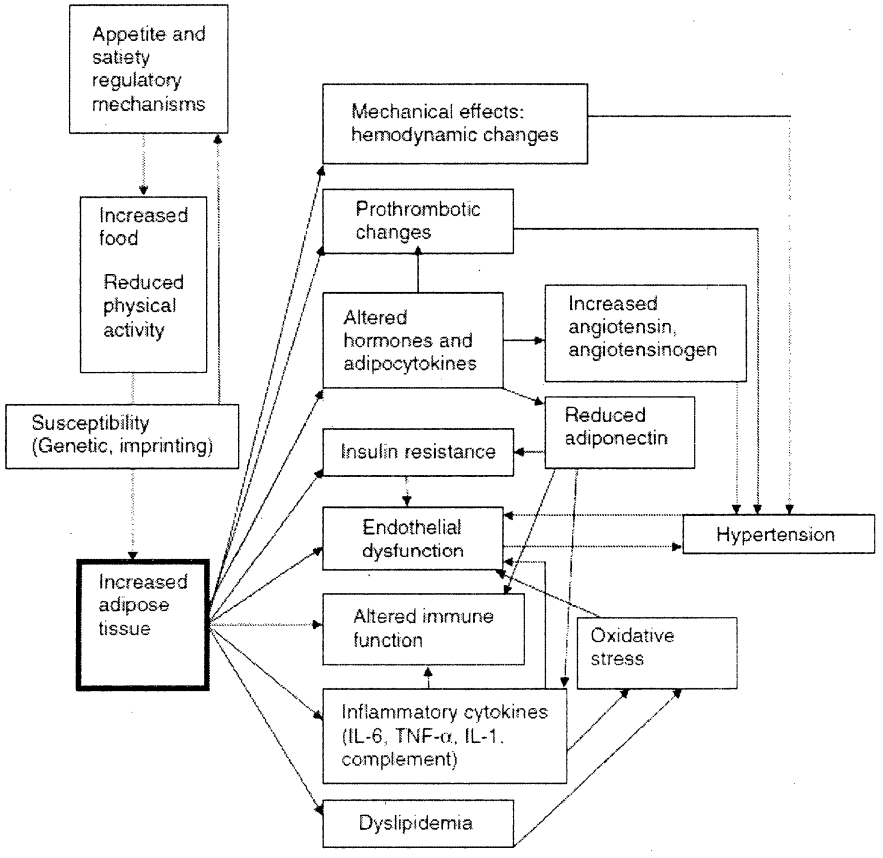

Figure 1.4 Schematic depiction of the relationship between excess adipose tissue the occurrence of chronic diseases and hypertension during pregnancy

(Callaway, et al., 2009).

Cardiovascular diseases and type 2 diabetes are common obesity related conditions linked to the increased levels of pro-inflammatory cytokines due to excess adipose tissue (Balistreri, Caruso, & Candore, 2010). Increased rates of pregnancy related hypertensive disorders were noted in women with gestational, type 1, and type 2 diabetes (Tanaka et al., 2007).

b. Smoking The mechanism regarding the reduction in preeclampsia risk as it relates to cigarette smoking during pregnancy remains unclear. It is speculated that the observed protection is due to changes in the balance of angiogenic factors. England and Zhang (2007) indicated that increases in pro-angiogenic factors and decreases in anti-angiogenic factors are responsible for the observed protective relationship of smoking against preeclampsia. Maternal blood levels of pro-angiogenic factors, specifically levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), have been observed to be lower in preeclamptic women (England & Zhang, 2007). It is suspected that smoking increases the placental expression of VEGF thus, increasing VEGF levels in the mother's blood which in turn reduces preeclampsia risk (England and Zhang, 2007). Another explanation given for the observed relationship between smoking and preeclampsia risk is that the components of tobacco smoke lowers blood pressure (Odegard et al., 2000).

While oxidative stress appears to be an important link between many maternal factors and the risk of preeclampsia, this is not the case with smoking, which through research has shown increases oxidative stress and reduces antioxidant levels in the blood,

the consensus among researchers is that it reduces the risk of preeclampsia (England & Zhang, 2007).

c. Prenatal and Preconception Care Weight screening is recommended during preconception visits through postpartum visits (Akkerman, 2012). In addition nutrition and weight counseling are recommended during preconception visits, nutrition should also be discussed at the first prenatal visit (Akkerman, 2012). Preconception care was included in the model because health professionals have the opportunity to identify maternal risk factors during prenatal visits, and provide counseling and education to pregnant women who are overweight/obese prior to pregnancy. The risk of preeclampsia may be decreased through weight management interventions.

d. WIC Enrollment in the WIC program was included in the model as a surrogate for maternal nutrition status, since qualification for enrollment is based on nutrition risk. Participation in the WIC program was expected to improve the nutrition status of participants by increasing access to nutrient rich foods. It was speculated that the nutrient rich foods provided by WIC packages would be helpful in combating inflammation, the oxidative stress component of preeclampsia, and reducing nutrient deficiencies associated with increased preeclampsia risk.

E. Significance to Preventive Care

Some of the factors contributing to preeclampsia risk and eclampsia occurrence appear to be modifiable through screening, early detection, and lifestyle interventions. Preventive Care Specialists are experts in disease prevention and management through risk reduction, employing methods such as weight and stress management. Therefore

Preventive Care Specialists have the opportunity to prevent and reduce adverse pregnancy outcomes due to preeclampsia and eclampsia through their clinical encounters with women of child-bearing age.

CHAPTER 2

REVIEW OF LITERATURE

A. Overview

The etiology of preeclampsia remains unclear thus the prevention, management, and treatment of the condition has been challenging (Kanasaki & Kalluri, 2009; Longo, Dola, & Pridjian, 2003; Serrano, 2006). Treating symptoms and early delivery remains the only treatment (Bell, 2010). Since there is no cure there is a need for recommendations to guide clinical and public health practice regarding the prevention, detection, and management of preeclampsia. This literature review focuses on the current body of research as it relates to preeclampsia and eclampsia and includes (a) diagnosis and screening, (b) maternal associated factors, (c) current strategies for prevention and management, and concludes with a summary and implications for future clinical practice and research. Every effort was made to conduct a comprehensive literature search to identify relevant research using electronic databases PubMed, Academic Search Premier, and Google Scholar.

B. Diagnosis and Screening of Preeclampsia

According to the National Heart Blood and Lung Institute's National High Blood Pressure Education Program four possible hypertensive conditions may occur during pregnancy: chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on existing hypertension, and gestational hypertension (Mustafa et al., 2012). Clinical protocol specifies that in order to correctly diagnose hypertension during pregnancy a patient must have a systolic blood pressure of 140mmHg or greater and a diastolic of 90mmHg or greater, measured twice, 20 minutes apart on two separate occasions

(Mustafa et al., 2012). Chronic hypertension is diagnosed when a woman presents with a blood pressure 140/90mmHg or greater prior to 20 weeks gestation or is known to have a history of hypertension and the hypertensive condition continues for more than 12 weeks after delivery (Mustafa et al., 2012; Wagner, 2004). Preeclampsia-eclampsia occur mid-pregnancy when elevated blood pressure is noted in the presence of at least 300mg/24hr proteinuria, and preeclampsia superimposed on existing hypertension means there is proteinuria in addition to preexisting hypertension (Mustafa et al., 2012). Gestational hypertension is characterized by the development of hypertension after mid-pregnancy, with no proteinuria and the return of normal blood pressure after delivery (Mustafa et al., 2012).

Further classification of preeclampsia is based on severity, allowing for further evaluation of a woman's risk. Mild preeclampsia is diagnosed when a woman presents with a $\geq$ 25mmHg increase in diastolic blood pressure and positive proteinuria on one occasion; moderate preeclampsia is signaled by a $\geq$ 25mmHg increase in diastolic blood pressure and positive proteinuria on two occasions; and severe preeclampsia is characterized by diastolic blood pressure $\geq$ 110mmHg, an increase in diastolic pressure of $\geq$ 25mmHg and positive proteinuria on three occasions or 500mg/24hrs (Odegard et al., 2000). A diagnosis of early onset preeclampsia is characterized by delivery before 34 weeks (Seed et al., 2011). Mbah et. al (2010) also used a similar classification, defining early onset as occurring before 34 weeks and late onset occurring at or after 34 weeks.

Due to the limited existing body of knowledge regarding the etiology of preeclampsia primary prevention and screening have proven challenging. Attempts are being made to identify screening tests that would predict the risk of developing

preeclampsia prior to the development of symptoms with high predictive accuracy in high-risk or low-risk women (Briceño-Pérez, Briceño-Sanabria, & Vigil-De Gracia, 2009).

In a meta-analysis of 34 studies mean arterial pressure was found to be a more accurate predictor of preeclampsia during the first and second trimester than systolic and diastolic blood pressure or an increase in blood pressure (Cnossen, Vollebregt, et al., 2008).

Delic and Stefanovic (2010) investigated which biomarkers may be most appropriate for predicting preeclampsia in the third trimester, comparing 113 preeclapmitc patients with 95 controls. Researchers correctly identified 79.6% preeclamptic patients with the use of uric acid and urea tests (Delic & Stefanovic, 2010). Including the additional biomarkers thrombocytes, hematocrit, aspartate aminotransferase, and leukocytes allowed researchers to correctly identify 83.8% of preeclamptic patients (Delic & Stefanovic, 2010). Researchers indicated that these tests could be used as a comprehensive laboratory test panel for predicting preeclampsia (Delic & Stefanovic, 2010). In a similar study, researchers were able to confirm preeclampsia, particularly early onset preeclampsia, by utilizing biomarkers the inhibin A, PlGF, and endoglin (Lambert-Messerlian et al., 2009).

The possibility of using Doppler technology to accurately predict preeclampsia has been explored by several researchers (Cnossen et al., 2009; Phupong et al., 2003). A review of several studies (n=219; 27 tests) by Cnossen and colleagues (2009) indicated that multiple studies confirmed that a BMI>34kg/m^2, alpha feto-protein, fibronectin and uterine artery Doppler measurements had 90% specificity, but only Doppler

measurements had a sensitivity over 60%. Phupong and colleagues (2003) observed that within a low risk population of pregnant women those with abnormal Doppler results were at higher risk of developing preeclampsia and giving birth to small for gestational age infants compared to women with normal Doppler results ($P<0.05$).

In a case control study conducted in Iraq, researchers compared the total, corrected and ionized calcium in 60 patients with preeclampsia, 30 in the second trimester and 30 in the third trimester, to a control group of healthy pregnant women (Al-Rubaye, 2010). The serum corrected total calcium, serum calculated ionized calcium, and actual calcium were significantly reduced in women diagnosed with preeclampsia in the third trimester ($p<0.001$) compared to healthy pregnant controls (Al-Rubaye, 2010). Additionally, lower serum corrected total calcium was observed in women diagnosed with preeclampsia in their second trimester ($p<0.001$) compared to the healthy controls (Al-Rubaye, 2010). The ionized calcium is used in the production of nitric oxide, and low ionized calcium in preeclamptics helps to explain the increased vasoconstriction (Al-Rubaye, 2010).

Due to the lack of consensus regarding the regular clinical use of Doppler technology and biomarkers for predicting preeclampsia, alternative screening methods have been considered. Generally, symptoms associated with preeclampsia include severe headache, nausea, and vomiting, and abnormal epigastric pain (Shakila Thangaratinam et al., 2011). Thangaratinam and colleagues (2011) conducted a review of several studies to assess how accurately maternal symptoms predicted complications in preeclamptic women. Headache was noted to have the highest sensitivity, followed by epigastric pain (S. Thangaratinam, Ismail, Sharp, Coomarasamy, & Khan, 2006). Nausea

and vomiting, epigastric pain and vision problems were noted to have the highest specificity (Shakila Thangaratinam et al., 2011).

C. Preeclampsia-Eclampsia Maternal Associated Factors

1. Role of Prenatal/Preconception Care and WIC (Women Infants and Children) Participation

Several Healthy People 2020 maternal and child health goals are aimed at preconception health behaviors such as increasing the number of women who receive preconception care (United States Department of Health and Human Services [HHS], Healthy People 2020, 2011). Additional objectives focus on pregnancy health behaviors such as: obtaining prenatal care at the beginning of the first trimester and obtaining adequate prenatal care (Healthy People 2020, 2011). Inadequate prenatal care as well as excess use of prenatal care was found to be associated with increased infant mortality among with high and low risk pregnancies (Chen, Wen, Yang, & Walker, 2007). Shi, Stevens, Wulu, Politzer and Xu (2004) noted that between 1996 -2001 only 60% of mothers receiving care at community health centers in the US were in their first-trimester of pregnancy.

Since early detection and treatment are important methods of preeclampsia and eclampsia management, the role of prenatal care and utilization of prenatal services remains an important factor for consideration. A review of hospital records of women with preeclampsia (n=685) delivering at King Fahad hospital in Saudi Arabia (n=27, 787) over a 10 year period indicated that those with preeclampsia were: (a) nulliparous, (b) mostly younger than 20 or older than 40 years, (c) had preterm births, and (d) more induced or cesarean deliveries (Al-Mulhim, Abu-Heija, Al-Jamma, & El-Harith, 2003).

Generally more complications for both mother and infant were found in women who did not have regular prenatal care (Al-Mulhim et al., 2003); stillbirths and deaths were associated with mothers who had no or irregular prenatal care (Al-Mulhim et al., 2003).

Although not directly related to preeclampsia risk, the utilization of WIC services positively affects maternal and infant outcomes. Special Supplemental Nutrition Program for Women Infants and Children is a federally mandated national program which provides food, nutrition education, and referrals to meet the medical and socioeconomic needs of eligible pregnant and, postpartum women, breastfeeding women, and infants and children under the age of five years old (Lazariu-Bauer et al., 2004).

An evaluation of the relationship between WIC participation and infant's birth weight in New York City indicated a direct association between length of participation and birth weight; this relationship was more pronounced in infants whose mothers were Black, Hispanic, or who had received either inadequate or no prenatal care (Lazariu-Bauer et al., 2004). In a cross-sectional study conducted in Washington State regarding the utilization of WIC, was found to be protective against adverse pregnancy outcomes such as preterm delivery, low birth weight and fetal death among high risk women, defined as those with a history of abortion, abnormal cervical health, inadequate prenatal care, or <12 years of education (El-Bastawissi, Peters, Sasseen, Bell, & Manolopoulos, 2007).

Not only has participation in WIC been shown to improve maternal and infant outcomes, but it is associated with improving infant mortality disparities between African Americans and Caucasians. Researchers compared WIC participants to non-WIC participants in Hamilton, Ohio over a three year period (Khanani, Elam, Hearn, Jones, &

Maseru, 2010). Infant mortality rates were lower for African American WIC participants than non-WIC participants and a reduction in infant mortality disparity between African Americans and Whites was also noted (Khanani et al., 2010). However, the results may have been confounded by higher rates of smoking among White mothers (Khanani et al., 2010).

Cramer and colleagues (2007) noted that a woman's decision to seek prenatal care, particularly among low income women in San Antonio, Texas, could not be easily predicted. Seeking care later in pregnancy was associated with barriers related to a woman's social context such as (a) less education, (b) unmarried or not living with a partner, and (c) unplanned pregnancies (Sunil et al., 2010). Factors such as (a) knowledge of the importance of prenatal care, (b) where to access care, and (c) financial means did increase the likelihood of seeking early prenatal for some women (Sunil, Spears, Hook, Castillo, & Torres, 2010).

2. Nutrition Status and Diet Quality

a. Antioxidants The relationship between maternal nutrition status and preeclampsia risk has been extensively studied. Researchers have indicated that several micro and macronutrients are associated with preeclampsia risk. Due to the oxidative stress component of preeclampsia antioxidant supplementation has been explored as an alternative treatment (Poston, Briley, Seed, Kelly, & Shannon, 2006). Nutrients can affect oxidative stress by increasing or decreasing free radicals or antioxidants, promoting the formation of free radicals, or interacting with antioxidant enzymes (Xu et al., 2009).

In a randomized controlled double blind placebo trial of pregnant women (n=29) diagnosed with low antioxidant status (superoxidedimutase [SOD]) level below 1102 U/g

Hb or 164 U/ml), received daily antioxidant supplements between 8-12 weeks of pregnancy (Rumiris, Purwosunu, Wibowo, Farina, & Sekizawa, 2006). Supplementation consisted of vitamins A (1000 IU); B6 (2.2 mg); B12 (2.2 μg); C (200 mg); and E (400 IU); folic acid (400 μg); N-acetylcysteine (200 mg); copper (2 mg), zinc (15 mg); manganese (0.5 mg), iron (30 mg); calcium (800 mg), and selenium (100 μg) (Rumiris et al., 2006). The control group (n=31) received iron (30 mg) and folic acid (400 μg) (Rumiris et al., 2006). Fewer cases of preeclampsia were observed in the supplementation versus control group (p = 0.043, OR = 0.18, 95% CI: 0.03, 0.92) (Rumiris et al., 2006). Researchers concluded that antioxidant supplementation was associated with better maternal outcomes in pregnant women with low antioxidant status and screening for low superoxidedimutase would be beneficial for preventing preeclampsia (Rumiris et al., 2006). These results contradicted a study conducted by Lindheimer and Sibai (2006), who observed negative outcomes in women supplemented with 1000mg of vitamin C and 400 IU of vitamin E. Differences in results indicate the lack of knowledge about correct dosing, which antioxidants or antioxidant combinations are best, and when supplementation should begin.

Lower levels of vitamin C and E have been noted in preeclamptic women (Poston et al., 2006), and a attempts have been made to establish the association between those vitamins and preeclampsia. In the Vitamin in Preeclampsia (VIP) study, a randomized control trial of 2,410 women with risk factors for preeclampsia received daily supplements of 1000mg of vitamin C, 400 IUs of vitamin E or placebo from the second trimester until delivery (Poston et al., 2006). Unfortunately, the incidence of preeclampsia remained similar in both groups, and in fact more low birth weight infants

were born to the women who received antioxidant supplementation (Lindheimer & Sibai, 2006; Poston et al., 2006).

One trial supplementing vitamin C at <26 weeks gestation in women with a history of previous abortion or preterm birth and who were considered high risk for preterm birth, resulted in no reduction of preeclampsia risk (Xu et al., 2009). Women classified as high and low risk for developing preeclampsia were evaluated in six trials testing the efficacy of vitamin C and E supplementation between weeks 12-20 weeks of gestation; however only one trial yielded significant results (Xu et al., 2009). Another trial utilized supplementation of vitamins C (500mg) and E (400 IU) daily, and 100mg of aspirin and 1g of fish oil three times weekly at <29 weeks and significant reduction in the occurrence of preeclampsia compared to the placebo group (Xu et al., 2009).

As mentioned earlier, oxidative stress is considered an important contributor to the development of preeclampsia, and in the body transition metals such as iron increase oxidative stress activity (Siddiqui, Jaleel, Kadri, Saeed, & Tamimi, 2011). A cross sectional study compared red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (Hct), red blood cell indices, and iron status parameters in 40 preeclamptic women and 80 healthy pregnant women (Siddiqui et al., 2011). The mean serum iron and ferritin were found to be higher in the preeclampsia group (Siddiqui et al., 2011).

b. Anemia and Iron Status Anemia has been implicated as a contributing factor to the development of preeclampsia. Supplementation with 27 mg of iron daily versus placebo at <13 weeks of gestation in healthy pregnant women resulted in no reduction of preeclampsia (Xu et al., 2009).

c. Calcium Calcium is one of the most extensively studied micronutrients and also one of the most promising in reducing preeclampsia risk. A review of 12 trials evaluating low calcium intake found that calcium supplementation was protective against preeclampsia in women with low calcium (Xu et al., 2009). This was similar to findings from a review conducted by Hofmeyr, Duley and Atallah (2007), in which observed reduction in preeclampsia occurrence were greatest for women at high risk (five trials, 587 women: RR: 0.22; 95% CI 0.12–0.42) and for those with low baseline calcium intake (seven trials, 10 154 women: RR: 0.36; 95% CI 0.18–0.70) (Hofmeyr et al., 2007). Reviewers concluded that adequate calcium supplementation is needed for prevention of preeclampsia but did not specify what "adequate" meant in terms of dosage.

Imdad, Jabeen and Bhutta (2011) completed a meta-analysis of the role of calcium supplementation in reducing the risk of gestational hypertensive disorders in developing countries. An inverse relationship between calcium supplementation and the development of hypertension was noted in both epidemiological and clinical studies but outcomes across trials were not consistent; baseline calcium levels and pre-existing risk factors seemed to be responsible for the inconsistency (Imdad et al., 2011).

d. Vitamin D Maternal vitamin D deficiency has been associated with several adverse pregnancy outcomes, including preeclampsia and childhood asthma (Finer et al., 2012). In a prospective cohort study conducted in Vancouver, Canada, serum 25-hydroxyvitatmin D (25OHD) was measured between 10 and 20 weeks gestation in 221 women at risk for preeclampsia (Shand et al., 2010). Seventy-eight percent of the women were considered vitamin D insufficient (25OHD< 75nmol/l) and

53% were vitamin D deficient (25OHD <50nmol/l) (Shand et al., 2010). No difference was found in the rates of preeclampsia, gestational hypertension, preterm birth or adverse pregnancy outcomes by 25OHD concentration (Shand et al., 2010). However, researchers were explicit about what maternal factors they controlled for in their analysis which may have contributed to their inability to detect a difference between the two groups.

Several methodological differences existed between the study conducted by Shand et al. (2010) and other studies exploring the role of vitamin D status in the development of preeclampsia. Serum 25OHD concentrations are measured at different weeks of gestation, and vitamin D supplementation is given to women at different time points in their pregnancy (Shand et al., 2010). This makes it difficult to determine the optimal timing for vitamin D supplementation on the reduction of preeclampsia risk. In the Shand et. al (2010) study other factors were associated with decreased risk of preeclampsia, such as exercise and dietary intake of calcium or long-chain n-3 fatty acids were not controlled for because the information was not available .

e. *Magnesium and Zinc* Less success has been noted regarding the role of zinc and magnesium supplementation during pregnancy and the risk of preeclampsia. Among seven trials investigating zinc versus no zinc with doses ranging from 20 to 44 mg daily or placebo between 15-27 weeks of gestation in normal pregnant women with normal and low zinc status, only one found that zinc supplementation significantly reduced the risk of preeclampsia (Xu et al., 2009). In two trials investigating the role of magnesium, no reduction of preeclampsia associated with magnesium supplementation,

but reviewers indicated that there may have been issues with the research methodologies (Xu et al., 2009).

f. Diet Quality No research was found to substantiate the use of fiber or protein in reducing the risk of preeclampsia, but there was evidence supporting the association between fat intake and blood lipid biomarkers and the preeclampsia. Dyslipidemia is common in women with this condition (Xu et al., 2009). Reduced high density lipoprotein (HDL) cholesterol as well as increases in triglycerides and low density lipoprotein (LDL) cholesterol and free fatty acids have been observed in women who developed preeclampsia before 20 weeks of gestation (Xu et al., 2009). Other nutrition related biomarkers associated with increased risk include (a) increased polyunsaturated (b) increased total free fatty acids, and (c) reduced n-3 fatty acids (Xu et al., 2009). Sodium restriction was not associated with reduction in preeclampsia (Xu et al., 2009).

In a case control study conducted by Reyes and colleagues, the nutrition status of 201 pregnant women with preeclampsia was compared to 201 healthy pregnant subjects and 201 non-pregnant healthy controls in Colombia (Reyes, Garcia, Ruiz, Dehghan, & López-Jaramillo, 2012). Serum glucose and lipids were obtained and nutrition status was assessed using food frequency questionnaires (Reyes et al., 2012). Compared to healthy pregnant controls, preeclamptic women had: (a) higher body mass index; (b) higher fasting glucose levels; (c) higher triglyceride levels; (d) lower high density lipoprotein cholesterol levels; and (e) higher energy, cereal and carbohydrate intake (Reyes et al., 2012). Higher odium and carbohydrate intake were associated with preeclampsia (Reyes et al., 2012).

In the Norwegian Mother and Child Cohort Study (MoBa) researchers investigated the association between dietary patterns during pregnancy and risk for preeclampsia (Brantsaeter et al., 2009; Meltzer et al., 2011). Study subjects were 23,423 nulliparious women who completed a general questionnaire at 15 weeks gestation and food frequency questionnaires at 17-22 weeks (Brantsaeter et al., 2009). Women who had high scores on a diet pattern which included mainly vegetables, plant foods and vegetable oils had a decreased risk (OR: 0.72; 95% CI: 0.62, 0.85) (Brantsaeter et al., 2009). Women whose diet consisted mainly of processed meat, salty snacks, and sweet drinks were at increased risk of developing preeclampsia (OR: 1.21; 95% CI: 1.03, 1.42) (Brantsaeter et al., 2009). These relationships were observed after adjusting for possible confounders such as maternal BMI, maternal height, education, smoking status, and hypertension prior to pregnancy, dietary supplement use, and total caloric intake (Brantsaeter et al., 2009).

3. Weight Status

Maternal obesity and excessive weight gain during pregnancy are associated with several poor maternal and infant outcomes such as macrosomia, very low birth weight, neural tube defects, preterm birth and cesarean delivery, preeclampsia and gestational hypertension (Derbyshire, 2008; Sahu, Agarwal, Das, & Pandey, 2007). The recommendations for weight gain during pregnancy from the Institute of Medicine (IOM) are as follows: 28-40 lbs for underweight women (BMI <19.8kg/m^2); 25-35lbs for normal weight women (BMI: 19.8-26 kg/m^2); 15-25 lbs for overweight women (BMI: 26.1-29kg/m^2); and at least 15 lbs for obese women (BMI>29kg/m^2) (Stotland et al., 2005). Maternal weight gain has also been associated with increased risk of adverse maternal

and fetal outcomes, including preeclampsia. Women who gained >25 lbs during pregnancy, above the IOM's recommendations were more likely to experience preeclampsia, cesarean delivery and macrasomia (Langford et al., 2011). Obese women who gained less than 15 lbs per the IOM recommendations were observed to have decreased risk of preeclampsia, cesarean deliveries, and large infants, and increased risk for giving birth to small infants (Kiel, Dodson, Artal, Boehmer, & Leet, 2007).

The relationship between excess weight and preeclampsia risk appears to transcend ethnicity. Increased risk for preeclampsia was associated with overweight (OR: 1.55; 95% CI: 1.30-1.86) and obese (OR: 3.10; 95% CI: 2.54-3.78) women who delivered babies in 10 public hospitals in Buenos Aires, Argentina (Hauger, Gibbons, Vik, & Belizan, 2008). A retrospective study with of 3,554 Korean women examined the relationship between pre-pregnancy BMI and gestational weight gain (Park et al., 2011). Compared to their normal weight counterparts, overweight women were found to have a higher risk of preeclampsia (adjusted OR: 2.4) and gestational diabetes (adjusted OR: 2.0) (Park et al., 2011).

4. Psychological Stress

Investigating the influence of maternal depression on birth outcomes Bansil and colleagues (2010) examined hospital discharge records from the 1998-2005 Nationwide Inpatient Sample (NIS) to obtain information regarding delivery related hospitalizations for select maternal and fetal outcomes by depression diagnosis. Women diagnosed with depression were more likely to have cesarean delivery, preterm labor, anemia, diabetes and preeclampsia or hypertension compared to those who were not

depressed, concluding that depression was associated with adverse maternal outcomes (Bansil et al., 2010).

In a community based cohort study, researchers in Amsterdam investigated the relationship between psychological stress in 12,377 women who filled out a questionnaire prior to 24 weeks gestation and 24 weeks after delivery (Vollebregt et al., 2008). Questionnaires and medical files were used to confirm diagnosis or gestational hypertension for women with hypertension and/or proteinuria, according to the International Society for the Study of Hypertension in Pregnancy guidelines (Vollebregt et al., 2008). Three questionnaires were used to assess psychosocial stress: work stress, anxiety, depression, and pregnancy related anxiety (Vollebregt et al., 2008). Researchers concluded that psychosocial stress in the first half of pregnancy does not influence the incidence of preeclampsia and gestational hypertension in nulliparous women (Vollebregt et al., 2008). However, these results may only be applicable to women living in Amsterdam during the first half of their pregnancy.

5. Smoking Status

The existing body of research reports an inverse association between maternal smoking and preeclampsia (Engel, Janevic, Stein, & Savitz, 2009). Researchers investigated the relationship between smoking and preeclampsia among 674,250 singleton pregnancies in New York City between 1995 and 2003, smoking was observed to be associated with a reduced risk of preeclampsia in women ≤ 30 years old (OR: 0.94; 95% CI: 0.90, 98) (Engel et al., 2009). Compared to women ≤ 20 years old, preeclampsia risk was greater with increasing age (Engel et al., 2009). Women ≥ 41 years old had greater preeclampsia risk (OR: 2.03; 95% CI: 1.88, 2.19) than those between ages 31 and

40 (OR: 1.22; 95% CI: 1.16,1.27) (Engel et al., 2009). Research concluded that smoking is only protective against preeclampsia, without pre-gestational hypertension among younger women.

England and Zhang (2007) conducted a review of 48 epidemiological studies conducted between 1959 and 2006 to investigate the association between cigarette smoking and the risk of developing preeclampsia. Researchers indicated that smoking is associated with reduced preeclampsia risk up to 50% regardless of parity, mild versus severe preeclampsia and single versus multiple gestation (England & Zhang, 2007).

6. Physical Activity

Physical activity has also been investigated to explore its associations with preeclampsia risk, and results in this area have been positive. Leisure time physical activity (LTPA), defined as exercise before and during pregnancy, was found to be protective against the development of gestational diabetes mellitus (GDM) and preeclampsia (Hegaard, Pedersen, Nielsen, & Damm, 2007). In a case control trial, researchers investigated the independent and combined effects of work and regular LTPA during early pregnancy on the risk of preeclampsia in 44 women and gestational hypertension in 172 women, compared to 2,422 control subjects (Saftlas, Logsden-Sackett, Wang, Woolson, & Bracken, 2004). Interviewers gathered information about time spent at work sitting, standing, walking, and engagement in exercise before and during pregnancy (Saftlas et al., 2004). Engaging in regular LTPA was shown to reduce preeclampsia risk (Saftlas et al., 2004). There was no consensus on frequency, intensity, and duration of exercise for reduction of preeclampsia risk.

7. Ethnicity

In the U.S., Black women have higher rates of preeclampsia than White women (Bryant, Seely, Cohen, & Lieberman, 2005). Researchers reviewed 1,355 medical records of Black and White women to determine whether the higher rates in Black women were due to higher rates of chronic hypertension in this group (Bryant et al., 2005). While hypertension during pregnancy occurred in 7.4% of Black women and 7.4% of White women (Bryant et al., 2005), in the absence of chronic hypertension, pregnant Black women with hypertension were more likely to be diagnosed with preeclampsia than White women (Bryant et al., 2005).

Associations between ethnicity and preeclampsia was examined using 902,460 birth records for the period 1995-2003 in New York City linked with hospital discharge data of US and foreign-born women (Gong, Savitz, Stein, & Engel, 2012). Researchers adjusted for maternal age, maternal education, parity, self-reported pre-pregnancy maternal weight, smoking during pregnancy, and year of delivery (Gong et al., 2012). East Asian women had the lowest risk of preeclampsia and Mexican women had the highest risk (Gong et al., 2012). No difference in risk was observed for U.S.- vs. foreign-born women, with the exception of foreign-born South-east Asian and Pacific Islanders who had increased risk of preeclampsia compared to those born in the U.S. (Gong et al., 2012). Researchers indicated their results should contribute to screening methods for preeclampsia risk, taking into account variations among ethnic groups (Gong et al., 2012).

Utilizing U.S. census data comprised of discharge data for 2.5 million women hospitalized for delivery 1993 through 2002, researchers examined the relationship

between preeclampsia and the neighborhood, socioeconomic status (SES), and ethnic subgroups in New York State (Tanaka et al., 2007). Black women were noted to have the highest number of diagnoses for all hypertensive disorders, and for preeclampsia alone regardless of neighborhood poverty levels (Tanaka et al., 2007). Black and Hispanic women were more likely than White women to have diabetes and were at higher risk of preeclampsia (Tanaka et al., 2007). Preeclampsia rates were higher in Black and Hispanic women with or without diabetes compared to their White counterparts (Tanaka et al., 2007).

8. Age

Adverse birth outcomes such as abnormal fetal development, delivery before 34 weeks, and still births are twice as likely to occur in women aged ≥ 35 years old (Delpisheh, Brabin, Attia, & Brabin, 2008). Extremes in age, young mothers (15 to 17 years old), and advanced maternal age (45 to 54 years old) were noted to have increased rates of gestational hypertension, and preeclampsia-eclampsia (Tanaka et al., 2007). Baker and Haeri (2012) indicated that among pregnant teens that developed preeclampsia had abnormal pre-pregnancy weight status and excessive weight gain were noted during pregnancy.

Several research studies have used different start points for advanced maternal age, some use >35 years and others have used >40 years (Salihu, Shumpert, Slay, Kirby, & Alexander, 2003). Older mothers are more likely to have experienced more illness or have a medical history which includes chronic conditions such as chronic hypertension, arthritis, cancer, depression, and heart attack, noted to be independent risk factors for fetal growth restriction (Delpisheh et al., 2008). Increased occurrence of preeclampsia

among older women could be due to chronic hypertension, and premature separation of the placenta may be caused by chronic hypertension and the effect of the aging process on arteries in the uterus (Salihu et al., 2003).

9. Other Maternal Factors

Parity, previous preeclampsia diagnosis, chronic conditions, and being pregnant with multiples are additional maternal factors associated with increased preeclampsia risk (Duckitt & Harrington, 2005). Examining the determinants of preeclampsia, gestational hypertension, and intrauterine growth researchers analyzed 39,615 records from the World Health Organization (WHO) Antenatal Trial (Villar et al., 2006). Previous maternal conditions such as diabetes, renal disease, preeclampsia, urinary tract infection, advanced maternal age, twin pregnancy, and obesity were associated with increased risk for preeclampsia and gestational hypertension (Villar et al., 2006).

Primiparity and nulliparity appear to be associated with increased risk of preeclampsia. Duckitt et al. (2005) noted in their review that nulliparity was associated with a threefold increase risk of preeclampsia. Results from a review of 26 published studies between 1966 and 2005 comparing the primiparous women to multiparous women indicated increased preeclampsia risk among primiparous women (Luo et al., 2007).

The recurrence rate for preeclampsia in the U.S. is 13-18% but this rate increases to approximately 47% when the previous episode of preeclampsia is diagnosed as severe and 65% if the severe preeclampsia occurs during the second trimester (Mendilcioglu, Trak, Uner, Umit, & Kucukosmanoglu, 2004). Previous preeclampsia in the first

pregnancy is associated with a seven-fold increase in preeclampsia risk in the second pregnancy (Duckitt & Harrington, 2005).

Results from five studies examining the risk of preeclampsia comparing twin pregnancies to singleton pregnancies indicated a summary unadjusted OR of 2.93 (95% CI 2.04 to 4.21) (Duckitt & Harrington, 2005). Increased preeclampsia risk was also noted for triplet pregnancies compared to twin pregnancies (OR 2.83, 95% CI 1.25-6.40) (Duckitt & Harrington, 2005).

D. Current Strategies for Prevention and Management

Several approaches have been adopted to prevent and manage preeclampsia once it has emerged. The main focus of primary prevention appears to be counseling and education (Shennan & Duhig, 2008). In order to ameliorate the non-modifiable factors such as maternal age, encouraging women to avoid becoming pregnant after age 35 may be prudent since it is speculated that the risk for developing preeclampsia increases 30% for every year after age 34 (Shennan & Duhig, 2008). Lifestyle counseling and education regarding weight management and weight loss is another primary prevention approach (Shennan & Duhig, 2008).

The secondary prevention approach focuses on identifying high risk women and treating them with prophylaxis. Antiplatelet medication, mainly aspirin, is one of the most widely used prophylaxis (Shennan & Duhig, 2008). Comparing moderate and high risk pregnant women who received aspirin to those who did not, the risk of preeclampsia was reduced by approximately 17% (RR=0.83, 95% CI: 0.77-0.89) (Shennan & Duhig, 2008). In clinical practice, aspirin is prescribed for women who are considered at high risk for developing preeclampsia, such as those with chronic conditions including

diabetes and chronic hypertension (Shennan & Duhig, 2008). Secondary prevention methods also involve calcium supplementation and aspirin during pregnancy in women with low calcium intake and who are at high risk of early development of preeclampsia (Briceño-Pérez et al., 2009).

Tertiary prevention approaches involve the prevention of injuries once preeclampsia has emerged (Shennan & Duhig, 2008). Antihypertensive agents are prescribed such as Labetolol and hydralazine for the management of blood pressure, to prevent progression to dangerous levels (Shennan & Duhig, 2008). Since preeclampsia progresses to eclampsia, a convulsive condition, anticonvulsants are prescribed. Magnesium sulfate remains the most commonly used anticonvulsant to date (Shennan & Duhig, 2008).

E. Conclusion

Based on the above review the etiology of preeclampsia is multi-factorial. Many research studies presented in the literature review reported associations but could not establish causation since the odds ratio or relative risk were used to estimate risk (Brantsæter et al., 2009; Duckitt & Harrington, 2005; Hauger et al., 2008; Hofmeyr et al., 2007; Luo et al., 2007; Rumiris et al., 2006). Establishing causation has also been difficult because multiple factors contribute to the development of preeclampsia.

There appears to be some consensus regarding low vitamin D and calcium status and increased preeclampsia risk. Therefore steps should be taken to establish evidenced based clinical protocols for the use of vitamin D and calcium to reduce preeclampsia risk in women deficient in these nutrients. Micronutrient supplementation and physical

activity are also areas which appear promising but require further research to establish clinical recommendations.

In general, micronutrient supplementation requires research to determine (a) which nutrients should be supplemented, (b) which women should receive supplements, (c) adequate supplement dosage, (d) when to initiate supplementation, and (e) duration of supplementation. A consensus is needed regarding frequency, intensity and duration of exercise for specific populations. In addition a number of studies reviewed were clinical trials; more of such studies are needed.

Doppler technology appears to be one of the screening tools most agreed upon among the various options for screening. The predictive accuracy of many tests have been questioned due to methodological issues; for example not all the studies defined preeclampsia according to clinical guidelines and not all abnormal test results used the same reference values or threshold values (Cnossen, Vollebregt, et al., 2008). With the consequences of early detection and missed diagnosis sometimes a matter of life and death, there is need for the development of high sensitivity tests which minimize false negatives (Cnossen, Morris, et al., 2008).

Future research is needed to learn more about the etiology of preeclampsia as well as modifiable maternal risk factors discussed in this literature review and study. Much is known about the association between preeclampsia and abnormal BMI as well as cigarette smoking, however, little is known about how other maternal factors affect these relationships, particularly WIC enrollment and prenatal care, which is the aim of this study.

CHAPTER 3

METHODS

A. Design

This cross-sectional study was conducted utilizing the San Bernardino Birth Cohort files from 2007-2008. The birth cohort files contain data for all live births that occurred in a calendar year, death information for those infants who were born in that year but subsequently died within 12 months of birth, and all fetal deaths that also occurred during that calendar year as well as detailed demographic information related to the child, mother, and father (CDPH, 2010). The files were obtained without personal identifiers. The San Bernardino county birth cohort data was originally obtained for demographic to be included in the National Children's Study.

The Center for Health Research at the Loma Linda University School of Public Health purchased 2007 to 2010 records from the California Health and Human Services Agency's Committee for the Protection of Human Subjects (CPHS) and California Department of Public Health Vital Statistics Advisory Committee (VSAC). Approval was obtained from Loma Linda University's Institutional Review Board to use 2007-2008 records for this study.

B. Participants

The participants were women living in San Bernardino County who gave birth from between 2007-2008. A total of 65,228 records were used in the analysis, 33,193 from 2007 and 32,035 from 2008. There were 705 preeclampsia cases in 2007 and 656 cases in 2008, and a total of 38 eclampsia cases between 2007 and 2008; 22 in 2007 and 16 in 2008. The following inclusion criteria was used: a) mother's place of residence was

in San Bernardino County at the time of delivery; b) mother gave birth to a singleton baby (i.e., not twins or triplets), and c) the length of gestation was greater than or equal to 20 weeks. Records with missing information were used but those with missing characteristics of interest were treated as missing, and no imputation was used.

C. Variables

1. Demographic Variables

The demographic and health variables of interest were maternal tobacco use, maternal pre-pregnancy BMI, IOM recommended weight gain, maternal age, maternal ethnicity, maternal years of education, WIC enrollment, trimester in which prenatal care began, and type of insurance. Frequencies and percentages were obtained for each demographic variable comparing preeclampsia cases to those cases without preeclampsia. Frequencies and percentages were also obtained for combined preeclampsia and eclampsia comparing cases with and without preeclampsia.

2. Exposure and Control Variables

The outcome variables of interest were preeclampsia and eclampsia, dichotomous variables, reported as yes or no on the birth certificate. The predictor variables are pre-pregnancy BMI, IOM pregnancy weight gain recommendations and maternal tobacco use. BMI was calculated using the height and pre-pregnancy weight provided by respondents on the birth certificate. Height was reported in feet and inches and weight was reported in pounds. The BMI variable was calculated by dividing the reported pre-pregnancy weight in pounds divided by the reported height inches squared multiplied by 703. BMI was stratified according to the Centers for Disease Control's classification: (a) underweight (< 18.5kgm/m^2); (b) normal (18.5kg/m^2-24.9kg/m^2); (c)

overweight (25.0-29.9kg/m^2); and (d) obese (> 30.0kg/m^2) (CDC, 2011). The recommendations for weight gain during pregnancy from the IOM based on pre-pregnancy BMI are as follows: 28-40 lbs for underweight women (BMI <19.8kg/m^2), 25-35 lbs for normal weight women (BMI: 19.8-26 kg/m^2), 15-25 lbs for overweight women (BMI: 26.1-29kg/m^2) and at least 15 lbs for obese women (BMI>29kg/m^2) (Stotland et al., 2005).

On the birth certificate, respondents were asked to report their smoking status and the average number of cigarettes or packs of cigarettes smoked per day: (a) three months before pregnancy, (b) first three months of pregnancy, (c) second three months of pregnancy, and (d) third three months of pregnancy. This information was used to classify smokers as never, pre-pregnancy smoker or prenatal smoker.

3. Confounder Variables

The following are confounders which were controlled for during the analysis. These variables were chosen based on the literature review.

- Maternal age (Langford et al., 2011; Mbah et al., 2010; Park et al., 2011).
- Prenatal care (Aliyu, Luke, Kristensen, Alio, & Salihu, 2010)
- WIC (Langford et al., 2011)
- Insurance (Langford et al., 2011; Park et al., 2011)
- Ethnicity (Langford et al., 2011; Mbah et al., 2010)

Maternal age was reported as a continuous variable but was stratified into three categories: (1) age < 18 years old, (3) 18-35 years old and, (3) >35 years old. Respondents reported the date of their first prenatal visit or whether they had no prenatal care. We then classified prenatal care into: (1) none, (2) 1st trimester, (3) 2nd trimester

and, (4) 3rd trimester. WIC enrollment was reported as yes or no. The birth certificate had four categories for type of insurance: (1) uninsured, (2) private, (3) Medi-Cal, and, (4) other. The categories for ethnicity were: Hispanic, non-Hispanic White, non-Hispanic Black, Asian/Pacific Islander and Other/Multi/Not-specified. Maternal years of education was stratified as follows: (a) 8th grade or less; (b) 9th-12th grade, no diploma and at least 9 years of education; (c) high school graduate, GED completed and at least 16 years of age; (d) some college credit but no degree and at least 17 years of age; (e) Associate degree and at least 18 years of age. Maternal education was not included in our multivariate model.

D. Data Analysis

Statistical Analysis Systems (SAS) software version [9.3] was used to analyze the data to investigate the relationships of interest and generate crude and adjusted odds ratio. There were not enough eclampsia cases to conduct separate analyses, therefore, analyses were conducted with preeclampsia cases and also combined preeclampsia and eclampsia cases.

Odds ratios were obtained from multivariate logistic regression analysis used to answer the following research questions. In the 2007-2008 San Bernardino County birth cohort data:

1. What is the relationship between maternal pre-pregnancy BMI and preeclampsia and eclampsia risk?
2. What is the relationship between IOM weight gain recommendations and preeclampsia and eclampsia risk?

3. What is the relationship between maternal smoking status and preeclampsia and eclampsia risk?

Several models were used to conduct the multivariate analysis. Three basic models were constructed to answer questions one through three a crude model, an age adjusted model and a multivariate model. Model 1, the crude models examined the effects of the exposure variables on the outcomes of interest; the age-adjusted model, Model 2 controlled for the effects of age; Model 3, the multivariate model, controlled for maternal age, maternal ethnicity, trimester in which prenatal care began, WIC enrollment, and insurance status. In addition, the WIC and prenatal care variables were added separately to age adjusted models. Finally, BMI was included in the multivariable model for question three to assess maternal smoking status on preeclampsia and eclampsia risk. Therefore, two multivariate models were constructed for question three, one without BMI and another including BMI.

E. Power Analysis

A power analysis was conducted for logistic regression using G*Power 3.1.1 software (Erdfelder & Faul, 1996) with the following parameters: *a priori*, two-tail, power of 0.8, and an alpha of 0.05. An odds ratio of 2.5 was selected based on previous research for questions one and two (Mbah et al., 2010; Park et al., 2011); 70 respondents were needed to answer those questions. An odds ratio of 0.7 was selected based on previous research for question three (Engel et al., 2009; Hammoud et al., 2005); approximately 395 respondents were needed to answer the question.

F. Study Limitations

There were several limitations to this study. Firstly, because this is a cross-sectional study it was not possible to evaluate causal relationships, thus reducing external validity. Second, findings are not generalizable to women living outside of San Bernardino County. Third, some of the information reported on the birth cohort records were self-reported such as height, pre-pregnancy weight and demographic information and could not be verified.

Since this study was based on secondary data analysis there are limitations regarding the variables chosen for analysis. The birth certificate contains questions such as the date prenatal care began, date of last prenatal care visit, and total number of prenatal visits during pregnancy. However, qualitative data regarding the quality of the prenatal visits, such as the kind of advice provided to patients during clinical encounter or questions the clinician asked, as well as the patient's impression of their clinician and visit were not available. This information would have been useful in assessing whether clinicians provided screening, counseling, or referrals for pre-pregnancy BMI>24.99kg/m^2, gestational weight gain or cigarette smoking. One variable, WIC enrollment, may not be reflective of consumption of WIC foods since client food diaries, which could have been useful for assessing program impact, might have shown detectable differences in preeclampsia/eclampsia risk based on diet quality or nutritional status, were not available. The diaries could have also been useful for assessing maternal alcohol use which is not captured on the birth certificate. It was not possible to control for when pre-pregnancy weight was measured because this information is not asked on the

birth certificate. Lastly, knowing when exactly smokers quit smoking and if they relapsed during pregnancy was not included on the birth certificate.

G. Research Ethics

The San Bernardino County Birth Cohort records were obtained without identifiers to protect the confidentiality of the study subjects. The Center for Health Research at the Loma Linda University School of Public Health adhered to the data security guidelines of the California Health and Human Services Agency's Committee for the Protection of Human Subjects (CPHS) and the California Department of Public Health Vital Statistics Advisory Committee (VSAC).

CHAPTER 4

FIRST PUBLISHABLE PAPER

Relationship Between Obesity Associated Preeclampsia-Eclampsia Risk, WIC and Prenatal Care Among Women In San Bernardino County

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Abstract

Background: An association between maternal obesity and preeclampsia has been found in several large US studies. Further investigation is needed to determine if similar associations remains for lower adiposity levels. In addition, women who gain too much weight during their pregnancy experience increased preeclampsia risk. The Women's, Infant, and Children program and early prenatal care remain primary prevention opportunities for addressing maternal overweight/obesity. These services may prove useful in preventing or reducing the occurrence of preeclampsia related to excess maternal body weight. The objective of our study was to examine the association between preeclampsia and excess maternal body weight in the analysis of all births occurring in San Bernardino County during 2007 and 2008. It is the largest county in the contiguous United States.

Methods: A population based study was conducted using information from the San Bernardino County birth cohort records for live births occurring 2007-2008 (N=65 228). Preeclampsia risk was estimated using logistic regression analyses based on pre-pregnancy body mass index and Institute of Medicine (IOM) gestational weight gain recommendations. Analyses were then conducted to explore investigate possible moderating effects of WIC enrollment and early prenatal care on pre-pregnancy BMI and IOM weight gain recommendations associated preeclampsia risk. These analyses were repeated for pregnancies affected by preeclampsia or eclampsia.

Results: Preeclampsia occurred in 2% and 1% of the population during 2007 and 2008 respectively. In 2007, women who were overweight or obese when they became pregnant had increased odds of developing preeclampsia; 1.41 [95% CI: 1.15, 1.74] and

2.32 [95% CI: 1.91, 2.80] respectively, compared to normal weight women. Women who gained more weight during their pregnancy than is recommended by the IOM were 1.61 [95% CI: 1.33, 1.94] times more likely to develop preeclampsia. Similar findings were noted when accounting for the effects of WIC enrollment and early prenatal care. Odds ratios for pregnancies affected by preeclampsia or eclampsia were similar to those noted for preeclampsia only.

Conclusion: Excessive maternal body weight based on pre-pregnancy BMI and IOM weight gain remain strongly associated with the increased occurrence of preeclampsia and eclampsia. This study offers alternatives for reducing preeclampsia occurrence through weight reduction. However, these alternatives warrant further investigation.

INTRODUCTION

Preeclampsia is a hypertensive condition of pregnancy diagnosed when a woman with no prior history develops hypertension and proteinuria after 20 weeks of gestation (1). Preeclampsia affects multiple maternal organs including the liver, brain, and kidneys (2, 3). Consequences of preeclampsia to the fetus include impaired fetal growth, premature birth, and death (4). Eclampsia is the onset of seizures related only to a preeclampsia diagnosis (1).

Maternal overweight and obesity, as well as nutrition status, are associated modifiable risk factors for preeclampsia (5, 6). Twenty percent of women in the U.S. are obese when they become pregnant; obese pregnant women (BMI >30kg/m^2) experience 2- 3 times the odds of developing preeclampsia compared to women of normal weight (7). Current clinical approaches to ameliorating the effects of preeclampsia are early detection and screening, medication management, and preterm delivery (3). However, these methods are focused on addressing this condition after it has been detected.

Preconception and prenatal care are primary prevention techniques which may prove to be beneficial in reducing weight associated preeclampsia risk through weight management (8). Preconception care can be described as care given to ensure that a woman is healthy prior to becoming pregnant, during and between pregnancies (9). The Select Panel on Preconception Care indicated that the purpose of preconception care should be to identify and modify maternal risk factors (biomedical, behavioral, and social) which may otherwise result adversely affect pregnancy outcomes (9) . Weight screening is recommended during preconception visits through postpartum visits (10).

Nutrition and weight counseling are recommended during preconception visits, and nutrition should also be discussed at the first prenatal visit (10).

Improving the nutritional status of pregnant women through nutrition education and counseling has proven to be effective in improving gestational weight gain, reducing anemia, increasing birth weight, and fewer preterm births (11). The effectiveness of these interventions increases when food and supplements are provided (11). The purpose of the Special Supplemental Nutrition Program for Women's, Infant, and Children (WIC) is to ensure that low income pregnant, breastfeeding, postpartum women, and infants and children up to age five are adequately nourished (12). The WIC program also has a WIC Farmers' Market Nutrition program to encourage increased intake of fruits and vegetables (13). Consumption of foods made available through WIC may help prevent and correct nutrient deficiencies linked to increased preeclampsia risk. Antioxidant rich fruits and vegetables may also ameliorate the effects of the oxidative stress component associated with preeclampsia (14). The goals for the prenatal care phase of the WIC program include the prevention of deficiencies in iron, calcium, vitamins A and C as well as protein and calories (12). In addition to providing supplemental foods this national program provides nutrition education as well as referrals for social and medical services for enrollees (12).

This study had three aims: (1) To explore the association between maternal pre-pregnancy BMI and risk preeclampsia and eclampsia, (2) To explore the association between the Institute of Medicine' (IOM) weight gain recommendations for pregnant women and risk of preeclampsia and eclampsia, and (3) To explore the association between prenatal care and enrollment in the WIC program and preeclampsia and

eclampsia. Early prenatal care and enrollment in the WIC program may prove to be valuable prevention tools for reducing the risk of preeclampsia and eclampsia associated with excess maternal body weight.

METHODS

Sample and participants

A total of 65,228 birth cohort records were used in the analysis of from women who gave birth in the county of San Bernardino in 2007 and 2008. Records were included in the analysis if (a) mother's place of residence was in San Bernardino County at the time of delivery; (b) the mother only gave birth to a singleton baby (i.e., not twins or triplets), and (c) the length of gestation was greater than or equal to 20 weeks. Records with missing information were used but those with missing characteristics of interest were treated as missing, and no imputation was used. The records contain data for all live births occurring in a calendar year, death information for infants born in that year but subsequently died within 12 months of birth, all fetal deaths that also occurred during that calendar year as well as detailed demographic information related to the child, mother, and father (15). The files were obtained without personal identifiers.

Variables

The outcome of interest was preeclampsia which was indicated as "yes" or "no" on the birth certificate. The exposure variables were maternal pre-pregnancy BMI and IOM weight gain recommendations for pregnant women. Confounders of interest were maternal age, ethnicity, years of education, WIC enrollment, trimester in which prenatal care began, and type of insurance. Maternal height and pre-pregnancy weight were self-reported on the birth certificate in feet and inches for height and in pounds for weight.

The BMI variable was calculated by dividing pre-pregnancy weight in pounds divided by the reported height inches squared multiplied by 703. BMI was stratified according to the Centers for Disease Control and Prevention's (CDC) BMI classification: (a) underweight (< 18.5kgm/m^2); (b) normal (18.5kg/m^2-24.9kg/m^2); (c) overweight (25.0-29.9kg/m^2); and (d) obese (> 30.0kg/m^2) (16). The recommendations for weight gain during pregnancy from the IOM based on pre-pregnancy BMI are as follows: 28-40lbs for underweight women (BMI <19.8kg/m^2); 25-35lbs for normal weight women (BMI: 19.8-26 kg/m^2); 15-25 lbs for overweight women (BMI: 26.1-29kg/m^2); and at least 15 lbs for obese women (BMI>29kg/m^2) (17). Respondents had the choice of selecting "yes" or "no" to indicate their WIC enrollment status. The standard U.S. birth certificate does not ask respondents to report the trimester of their first prenatal visit; therefore, the date of last normal menses and first date prenatal care began were used to calculate the trimester in which respondents began prenatal care. This calculation is often used for this purpose (18).

Data Analysis

Statistical Analysis Systems (SAS) [version 9.3] was used to analyze data (19). Logistic regression analyses were conducted to assess maternal associated preeclampsia or eclamplsia risk. A total of 22 preeclampsia cases were noted in 2007, and 16 cases in 2008. As a result the study had two outcomes: preeclampsia only and preeclampsia or eclampsia. Three models were used for the logistic regression analyses. Model 1 yielded a crude odds ratio (OR); model 2 an age adjusted OR, and model 3 was multivariate model, controlling for age, maternal ethnicity, trimester prenatal care began, and WIC enrollment and insurance status. To observe the effects of WIC enrollment and prenatal

care on preeclampsia risk we used age adjusted models. These analyses were conducted separately for 2007 and 2008.

RESULTS

The study population demographic characteristics are shown in Tables 1 and 2. In Table 1, of the 32 488 deliveries during 2007, 2.12% were affected by preeclampsia and 1.01% of the 32 035 deliveries in 2008 were affected by preeclampsia. The proportion of preeclampsia was highest among 18-39 year old women, Hispanic women, and women who completed high school (12 years of education). In 2007, 2.19% of the deliveries were affected by either preeclampsia or eclampsia, while 2.10% were affected by preeclampsia or eclampsia in 2008. Patterns regarding the occurrence of preeclampsia or eclampsia as they relate to age, ethnicity and years of education were similar to those for preeclampsia only.

Table 1. Demographic characteristics of mothers with preeclampsia versus no preclampsia in San Bernardino County in 2007 and 2008

	2007			2008		
n (%)	Total	No Preeclampsia	Preeclampsia	Total	No Preeclampsia	Preeclampsia
Occurrence	33193	32488 (97.88)	705 (2.12)	32035	31379 (97.95)	656 (1.01)
Maternal Age						
< 18 Years	1422	1391 (4.28)	31 (4.40)	1317	1293(4.12)	24 (3.77)
18-<35 Years	27918	27376 (84.27)	542 (76.88)	26886	26373 (84.05)	513 (78.20)
35 Years or older	3851	3719 (11.45)	132 (18.72)	3832	3713 (11.83)	119 (18.14)
Mother's Race/Ethnicity						
Hispanic	20059	19664 (60.04)	395 (56.03)	19213	18840 (60.04)	373 (56.86)
Non-Hispanic white	8218	8028 (24.71)	190 (26.95)	8013	7837 (24.98)	176 (26.83)
Non-Hispanic black	2800	2712 (8.35)	88 (12.48)	2756	2685 (8.56)	71 (10.82)
Asian/Pacific Islander	1925	1897 (5.84)	28 (3.97)	1824	1796 (5.72)	28 (4.27)
Other/Multi/Unknown	191	187 (0.58)	5 (0.69)	229	221 (0.70)	8 (1.19)
Mother's Years of Education						
0-8 Years	2360	2311 (7.17)	49 (6.98)	2045	2010 (6.46)	35 (5.39)
9-11 Years	7831	7706 (23.91)	125 (17.81)	7504	7357 (23.66)	147 (22.65)
12 Years	11145	10886 (33.77)	259 (36.89)	10399	10173 (32.71)	226 (34.82)
13-15 Years	7445	7254 (22.51)	191 (27.21)	7699	7534 (24.23)	165 (25.42)
16 Years or More	4153	4075 (12.64)	78 (11.11)	4102	4026 (12.95)	76 (11.71)
Principal Source of Payment for Prenatal Care						
Uninsured	1084	1061 (3.27)	23 (3.26)	888	871 (2.78)	17 (2.53)
Private Insurance	13920	13684 (42.12)	236 (33.48)	13295	13078 (41.68)	217 (33.08)
Medi-Cal	16236	15863 (48.83)	373 (52.91)	15844	15486 (49.35)	358 (54.57)
Other	1953	1880 (5.79)	73 (10.35)	2008	1944 (6.20)	64 (9.76)

Table 2. Frequency and percentages of demographic characteristics of mothers with combined preeclampsia or eclampsia in San Bernardino County in 2007 and 2008

	2007			2008		
n (%)	Total	No Preeclampsia or Eclampsia	Combined Preeclampsia or Eclampsia	Total	No Preeclampsia or Eclampsia	Combined Preeclampsia or Eclampsia
Occurrence	33193	32466 (97.81)	727 (2.19)	32035	31363 (97.90)	672 (2.10)
Maternal Age						
< 18 Years	1422	1390 (4.28)	32 (4.40)	1317	1293 (4.12)	24 (3.57)
18-<35 Years	27918	27357 (84.27)	561 (77.17)	26886	26360 (84.05)	526 (78.27)
35 Years or older	3851	3717 (11.45)	134 (18.43)	3832	3710 (11.83)	122 (18.15)
Mother's Race/Ethnicity						
Hispanic	20059	19655 (59.21)	404 (55.57)	19213	18830 (60.04)	383 (56.99)
Non-Hispanic white	8218	8022 (24.71)	196 (26.96)	8013	7836 (24.98)	177 (26.34)
Non-Hispanic black	2800	2706 (8.33)	94 (12.93)	2756	2682 (8.35)	74 (11.01)
Asian/Pacific Islander	1925	1897 (5.84)	28 (3.85)	1824	1794 (5.72)	30 (4.46)
Other/Multi/Unknown	191	186 (0.57)	5 (0.69)	229	221 (.70)	8 (1.19)
Mother's Years of Education						
0-8 Years	2360	2309 (7.17)	51 (7.04)	2045	2009 (6.46)	36 (5.41)
9-11 Years	7831	7699 ((23.90)	132 (18.23)	7504	7352 (23.65)	152 (22.86)
12 Years	11145	10877 (33.77)	268 (37.02)	10399	10169 (32.71)	230 (34.59)
13-15 Years	7445	7251 (22.51)	194 (26.60)	7699	7529 (24.22)	170 (25.56)
16 Years or More	4153	4074 (12.65)	79 (10.91)	4102	4025 (12.95)	77 (11.58)
Principal Source of Payment for Prenatal Care						
Uninsured	1084	1060 (3.26)	24 (3.30)	888	871 (2.78)	17 (2.53)
Private Insurance	13920	13676 (42.12)	244 (33.56)	13295	13705 (41.69)	220 (32.74)
Medi-Cal	16236	15851 (48.82)	385 (52.96)	15844	15473 (49.34)	371 (55.21)
Other	1953	1879 (5.79)	74 (10.18)	2008	1944 (6.20)	64 (9.52)

Odds ratios for the associations between maternal pre-pregnancy BMI and IOM weight gain recommendations and preeclampsia/preeclampsia or eclampsia are illustrated in Tables 3 and 4, respectively. Underweight women experienced a 51% reduction in preeclampsia occurrence during 2007 compared to women with normal pre-pregnancy BMI. Excess weight increased the likelihood of the occurrence of preeclampsia in a graded manner, indicating increased occurrence with increasing BMI. The odds of developing preeclampsia in 2007 and 2008 were approximately 1.41-1.90 (multivariate

adjusted models) and 2.32-2.83 (multivariate adjusted models) for overweight and obese women respectively, compared to women with normal pre-pregnancy BMI. Underweight women experienced a similar decrease in preeclampsia or eclampsia occurrence compared to developing preeclampsia only. Overweight and obese women had similar multivariate adjusted odds of developing preeclampsia or eclampsia as compared to the odds of developing preeclampsia only.

Table 3. Crude, Age-adjusted, and Multivariable odds ratios with 95% CI for preeclampsia outcomes among mothers in San Bernardino County in 2007 and 2008

	2007			2008		
	Crude	Age-Adjusted	Multivariable	Crude	Age-Adjusted	Multivariable
Mother's Pre-pregnancy BMI						
Under- weight	**0.49 (0.29, 0.83)**	**0.50 (0.30, 0.84)**	**0.49 (0.29, 0.82)**	**0.92 (0.59, 1.44)**	0.94 (0.60, 1.46)	0.91 (0.58, 1.43)
Normal Weight			1.00 (Reference)			
Over- weight	**1.41 (1.15, 1.72)**	**1.39 (1.13, 1.70)**	**1.41 (1.15, 1.74)**	**1.88 (1.52, 2.32)**	**1.86 (1.50, 2.30)**	**1.90 (1.53, 2.35)**
Obese	**2.32 (1.93, 2.80)**	**2.32 (1.92, 2.79)**	**2.32 (1.914, 2.80)**	**2.81 (2.30, 3.42)**	**2.78 (2.28, 3.39)**	**2.83 (2.31, 3.47)**
IOM Qualitative Weight Gain						
Too Little	0.83 (0.68, 1.00)	**0.80 (0.67, 0.97)**	**0.82 (0.67, 0.99)**	1.00 (0.90, 1.34)	1.08 (0.89, 1.31)	1.00 (0.90, 1.34)
Just Right			1.00 (Reference)			
Too Much	**1.63 (1.35, 1.97)**	**1.64 (1.36, 1.98)**	**1.61 (1.33, 1.94)**	**1.86 (1.52, 2.28)**	**1.89 (1.54, 2.31)**	**1.83 (1.49, 2.24)**

Multivariable - Adjusted for age, race/ethnicity, WIC utilization, insurance status, and month prenatal care began. CI= confidence interval.

Table 4. Crude, Age-adjusted, and Multivariable odds ratios with 95% CI for preeclampsia or eclampsia outcomes among mothers in San Bernardino County in 2007 and 2008

	2007			2008		
	Crude	Age-Adjusted	Multivariable	Crude	Age-Adjusted	Multivariable
Mother's Pre-pregnancy BMI						
Under- weight	**0.52 (0.31, 0.86)**	**0.52 (0.31, 0.86)**	**0.51 (0.30, 0.84)**	0.89 (0.57, 1.38)	0.90 (0.58, 1.40)	0.87 (0.56, 1.36)
Normal Weight	1.00 (Reference)					
Over- weight	**1.42 (1.16, 1.74)**	**1.40 (1.14, 1.71)**	**1.43 (1.16, 1.75)**	**1.85 (1.50, 2.28)**	**1.83 (1.48. 2.25)**	**1.86 (1.51, 2.30)**
Obese	**2.37 (1.97, 2.84)**	**2.36 (1.97, 2.84)**	**2.36 (1.96, 2.84)**	**2.72 (2.24, 3.31)**	**2.69 (2.21. 3.27)**	**2.74 (2.24, 3.35)**
IOM Qualitative Weight Gain						
Too Little	0.82 (0.69, 1.00)	**0.81 (0.672,0.98)**	**0.82 (0.68, 0.99)**	1.10 (0.90, 1.33)	1.08 (0.89, 1.31)	1.10 (0.90, 1.34)
Just Right	1.00 (Reference)					
Too Much	**1.63 (1.35, 1.95)**	**1.64 (1.36, 1.97)**	**1.60 (1.33, 1.92)**	**1.86 (1.53, 2.27)**	**1.89 (1.55, 2.31)**	**1.83 (1.50, 2.24)**

Multivariable - Adjusted for age, race/ethnicity, WIC utilization, insurance status, and month prenatal care began.

The odds ratio changed slightly across BMI categories when WIC and prenatal care enrollment were added to the age adjusted model. In 2007, the odds of developing preeclampsia was 0.50 [95% CI:0.30,0.85] for underweight women; 1.37 [1.12,1.69] for overweight women and 2.30 [1.91,2.78] for obese women compared to women with normal weight before pregnancy. During 2008 overweight women had an increased odds of 1.87 [1.51,2.32] and obese women had 2.78 [2.28,3.40] increased odds of developing preeclampsia compared to women with normal pre-pregnancy BMI. The odds of developing preeclampsia or eclampsia in 2007 was 0.53 [0.31,0.87] for underweight women, 1.39 [1.13,1.70] and 2.35 [1.95,2.86] for overweight and obese women respectively, compared to women with normal weight. In 2008, the odds were 1.84 [1.49,2.27] and 2.70 [2.21,3.29] for overweight and obese women respectively, compared to women with normal pre-pregnancy BMI.

Similar findings regarding the occurrence of preeclampsia or eclampsia were noted in 2007 when adding WIC and prenatal care enrollment separately to the age adjusted model. Age adjusted odds for the occurrence of preeclampsia or eclampsia were 0.52 [0.31,0.87] for underweight women, 1.41 overweight [1.15,1.72] and 2.38 [1.98,2.87] for obese compared to normal weight women. Increased odds of developing preeclampsia or eclampsia were noted among overweight 1.84 [1.49,2.27] and obese women 2.69 [2.21,3.28] compared to those with a pre-pregnancy BMI within normal range.

During 2007, women who gained too little weight experienced an 18% decrease in the likelihood of preeclampsia occurrence compared to those who were within IOM weight gain recommendations after multivariate adjustment. After adjusting for

confounders, women who gained more than IOM recommendations were approximately 1.63-1.83 more likely to develop preeclampsia during pregnancy compared to those whose weight gain were within IOM recommendations. Similar odds ratios were noted when combining preeclampsia and eclampsia cases. The odds of developing preeclampsia after adding prenatal care to the age adjusted model were 0.81[0.67,0.98] for those who gained less than IOM recommendations and 1.65 [1.37,2.00] for those gaining more than IOM recommendations in 2007. Weight gain above IOM recommendations was associated with 1.86 [1.52,2.28] increased odds compared to those who gained the recommended amount of weight during pregnancy. Similar results were noted when adjusting for WIC enrollment in the age adjusted model. During 2007 gaining less weight than is recommended by IOM was associated with a 19% [0.67,0.99] decreased likelihood of developing preeclampsia, and gaining more than is recommended by the IOM increased odds by 1.64 [1.36,1.98] for compared to whose weight followed IOM recommendations. In 2008 gaining weight above IOM recommendations increased the likelihood of developing preeclampsia (OR: 1.89 [1.54,2.31]). Finally, the odds for preeclampsia or eclampsia related to WIC enrollment during 2007 was 0.82 [0.68, 99] for women who gained less than the recommended amount of weight, 1.64 [1.36,1.97] for those gaining more than is recommended; in 2008 the odds for those who gained more than is recommended was 1.89 [1.55,2.31].

DISCUSSION

The present study provides further evidence regarding preeclampsia risk and maternal weight status. In particular it demonstrates the strong relationship between preeclampsia occurrence and excess maternal body weight. This study also attempted to

determine possible primary prevention solutions for ameliorating the occurrence of overweight and obesity associated preeclampsia, particularly enrollment in the WIC program and early prenatal care.

Similar studies examining the relationship between maternal weight status and preeclampsia risk also used birth cohort or hospital records (20-23). Pre-pregnancy BMI and gestational weight gain are known to be associated with adverse fetal and maternal outcomes including preeclampsia (24). Findings from this study regarding preeclampsia and maternal pre-pregnancy BMI are similar to other studies examining the relationship between preeclampsia and maternal BMI (25, 26). Researchers have observed increased preeclampsia risk with increasing BMI in similar studies (25, 26). Increased preeclampsia risk has also been observed among women who gain above the IOM weight recommendations (20, 27).

This study was not able to confirm that WIC and early prenatal care are moderators of the relationship between maternal weight status and preeclampsia risk. Researchers have suggested that increased preeclampsia risk based on maternal overweight and obesity may partly be due to the increased inflammation and oxidative stress associated with increased adipose tissue (28). Conflicting evidence exists from clinical trials regarding the use of antioxidant supplementation to reduce preeclampsia risk (29, 30). Because the risk factors for preeclampsia include obesity mediated by oxidative stress and nutrient deficiencies it was hypothesized that WIC enrollment and early prenatal care could provide opportunities during clinical encounters to: (a) assess weight status, (b) provide weight counseling based on the IOM recommendations, (c) prevent excessive weight gain, (d) correct and prevent nutrition deficiencies, and (e)

improve nutrition status by encouraging intake of antioxidant rich foods to ameliorate the oxidative stress component of preeclampsia. Obesity screening, diagnosis and weight counseling among women of reproductive age in primary care settings are low warranting that such practices be conducted in other healthcare settings (31).

STRENGTHS AND LIMITATIONS

On strength of this study is that it is one of the few known studies to explore how WIC and early prenatal care could moderate occurrence of maternal overweight or obesity associated preeclampsia. One limitation of the study is that it examined data retrospectively, thus restricting how information was collected and the type of data available for analyses. Prenatal care data gathered: the date of the first and last prenatal care visit, and the total number of prenatal visits. Prior research has used gestational age at delivery, month prenatal care was initiated, and total number of prenatal visits to calculate an adequacy index (31). The analysis exploring the effect of prenatal care could have been improved by using similar methodology. Early prenatal care was not useful regarding early diagnosis and screening of preeclampsia because this condition is diagnosed after 20 weeks of pregnancy. For this study, we focused on prenatal care in the context of addressing preeclampsia risk associated with excess body fat and nutrient deficiencies.

Another limitation is that WIC enrollment was recorded as a dichotomous variable, either yes or no. However, since diet quality and nutritional status of WIC enrollees varies, WIC enrollment alone may not be reflective of actual food consumption; enrollment was used as a surrogate for nutrition status since no food diaries from WIC enrollees were available for review. Food diaries would have been useful for assessing

the impact of WIC, particularly the respondents' nutrition status and diet quality with preeclampsia risk. Additional limitations included lack of information regarding maternal alcohol and illicit drug use and when enrollment in WIC began.

CONCLUSION

Results of this study confirm the increased risk associated with excess maternal body weight and preeclampsia risk. Our hypothesis about the enrollment in the WIC program or early prenatal care and overweight or obesity related preeclampsia risk was not confirmed. However, the results may serve to generate further hypothesis and investigation about non-clinical methods of reducing preeclampsia risk. Future studies seeking to explore the relationship between prenatal care and overweight or obesity related preeclampsia risk should include prenatal care adequacy indices to compare prenatal care adequacy with preeclampsia risk. We recommend a prospective study which includes measures to assess nutrition status, diet quality, weight screening, and how often a practitioner discusses weight status or provides referrals for weight management. In addition qualitative information should also be gathered to assess the type of weight management counseling practitioners provide.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CHAPTER 5

SECOND PUBLISHABLE PAPER

Maternal Cigarette Smoking Status and Preeclampsia and Eclampsia Risk among Women in San Bernardino County

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Abstract

Objectives: Consistent research findings exploring the relationship between maternal cigarette smoking and preeclampsia occurrence indicate that women who smoked during pregnancy experienced a reduction in the development of preeclampsia. The aim of our study was to examine the relationship between maternal cigarette smoking and the likelihood of preeclampsia or eclampsia in the analysis of San Bernardino County birth cohort data. In addition we examined how the trimester that prenatal care began and enrollment in the Women Infants and Children Program (WIC), interventions commonly used to prevent adverse birth outcomes could possibly moderate preeclampsia or eclampsia occurrence based on smoking status. It is the largest county in the contiguous United States.

Methods: This cross-sectional study utilized 65,288 birth cohort records from San Bernardino County between 2007 and 2008. Logistic regression analyses were conduced to explore the association between preeclampsia or eclampsia occurrence and maternal smoking status.

Results: Significant findings were noted for 2007 age adjusted models. Preeclampsia was 31% [95% CI: 0.50, 0.94] less likely to occur among never smokers compared to women who smoked during pregnancy. The 2007 age adjusted odds ratio for preeclampsia or eclampsia for women who never smoked was 0 0.67 [95% CI: 0.49, 0.92]. Similar findings were noted for WIC and prenatal care. No significant associations were noted between preeclampsia or eclampsia occurrence and smoking cessation.

Conclusion: Study results indicated contrary findings regarding maternal cigarette use and preeclampsia occurrence compared to existing research in this area. Currently a large

body of research evidence suggests an inverse relationship between cigarette smoking during pregnancy and preeclampsia occurrence. Smoking cessation at recognition of pregnancy was not effective for the prevention of preeclampsia. Further research is needed to explore the relationship between maternal cigarette smoking habits and preeclampsia occurrence.

INTRODUCTION

Several adverse reproductive, pregnancy and fetal outcomes are associated with maternal cigarette smoking during and after pregnancy. These adverse outcomes include spontaneous abortions, premature birth, low infant birth weight, Sudden Infant Death Syndrome (SIDS) and birth defects (1-3). Additional concerns include difficulty conceiving, longer hospital stays due to increased infant morbidity and infant mortality (4). Among the preventable causes attributed to female morbidity and mortality in the United States, cigarette smoking remains the most preventable (5). Smoking is also the most preventable maternal factor associated with infant mortality and morbidity (1). Second hand smoke (SHS) is also associated with adverse infant outcomes such as increased risk of developing respiratory distress syndrome and increased NICU admissions (6).

Changes in maternal smoking habits have also been noted due to increased awareness of the harmful effects of smoking during pregnancy. Between 1989 and 2004 there has been a 48% decrease in number of women who reported smoking during pregnancy (2). However, in the United States during 2008, 13% of women reported smoking during the last three months of pregnancy among women who smoked three months before pregnancy, 45% of women quit during pregnancy but approximately 50% began smoking within six months of delivery (4).

Despite the harmful reproductive, pregnancy and fetal outcomes associated with cigarette smoking research evidence indicates that cigarette smoking may have the opposite effect on preeclampsia risk. It has been suggested that smoking and preeclampsia act synergistically in lowering infant birth weight but little research

evidence exists to support this suggestion (7). Research evidence consistently point to the protective effects of cigarette smoking against preeclampsia (8). The observed protection of cigarette smoking against preeclampsia risk appears to be related to the products of combustion such as carbon monoxide rather than the nicotine which is also found in smokeless tobacco (9). Among cigarette smokers, heavy smokers (>9 cigarettes per day) experienced a greater reduction in preeclampsia and gestational hypertension risk compared to light smokers (1 to 9 cigarettes per day) (9). This dose dependent relationship was observed to be weaker among overweight and obese women (8).

The mechanism regarding the reduction in preeclampsia risk and smoking remains unclear. It is speculated that the observed protection is due to changes in the balance of angiogenic factors, increased pro-angiogenic factors and decreased anti-angiogenic factors (10). Another explanation given for the observed relationship between smoking and preeclampsia risk is that some components of tobacco smoke may lower blood pressure (7). Oxidative stress appears to be an important link between many maternal factors and the risk of preeclampsia (11-13). Smoking increases oxidative stress and reduces antioxidant levels in the blood yet consensus among researchers is that smoking reduces the risk of preeclampsia (8, 10, 14).

Preconception and prenatal care and the WIC program are valuable health promotion approaches to improving pregnancy and birth outcomes. Preconception care was noted to be associated with maternal health promoting behaviors such as pre-pregnancy multivitamin use, obtaining prenatal care during the first trimester and abstinence from alcohol use prior to becoming pregnant (15). Preconception and prenatal encounters allows for health professionals to identify and discuss maternal risk factors

such as smoking status with their patients. WIC is a national program providing supplemental food and nutrition education to pregnant, breastfeeding, postpartum women and children from birth to age five meeting income requirements (16). The goals for prenatal care phase of the WIC program include the prevention of nutrient deficiencies (16). Besides improvement in nutrition status enrollment in WIC has been shown to be associated with maternal smoking habits. Women who enrolled in WIC the first trimester and obtained prenatal care in the first trimester were more likely to decrease or quit smoking compared to those who enrolled later in their pregnancy (1, 2).

The purpose of this study was to investigate the association between maternal cigarette smoking and the occurrence of preeclampsia. We also attempted to explore how enrollment in the WIC program and the time prenatal care began could possibly moderate the association.

METHODS

Sample and participants

A total of 65 228 birth cohort records were used in the analysis reflecting all live births occurring in 2007 and 2008 in San Bernardino County. Records were included in the analysis if (a) mother's place of residence was in San Bernardino County at the time of delivery; (b) the mother only gave birth to a singleton baby (e.g., not twins, triplets), and (c) the length of gestation was greater than or equal to 20 weeks. Records with missing information were used but those with missing characteristics of interest were treated as missing, no imputation was used. The records contain data for all live births occurring in a calendar year, death information for those infants who were born in that year but subsequently died within 12 months of birth, and all fetal deaths that also

occurred during that calendar year as well as detailed demographic information related to the child, mother, and father (California Department of Public Health, 2010) . The files were obtained without personal identifiers.

Variables

Two outcomes of interest were preeclampsia which was recorded as "yes" or "no" and eclampsia, "yes" or "no". The exposure variable was maternal smoking status. Respondents were asked to indicate the number of cigarettes or packs of cigarettes they smoked three months before pregnancy, first three months of pregnancy, second three months of pregnancy, and third trimester of pregnancy. They were instructed to enter "0" if they did not smoke cigarettes during this period. For the purpose of the study maternal tobacco use categorized as never smoked, pregnancy smoker and prenatal smoker. Prenatal smoker (women who smoked during pregnancy) was selected for the reference category. Confounders of interest were maternal age, maternal ethnicity, maternal pre-pregnancy BMI, WIC enrollment, trimester prenatal care began, and type of insurance. The BMI variable was calculated by dividing pre-pregnancy weight in pounds divided by the reported height inches squared multiplied by 703. BMI was stratified according to the Centers for Disease Control BMI classification: (a) underweight (< 18.5kgm/m^2), (b) normal (18.5kg/m^2-24.9kg/m^2), (c) overweight (25.0-29.9kg/m^2), and (d) obese (> 30.0kg/m^2) (CDC, 2011). The standard United States birth certificate does not ask respondents to report the trimester they began prenatal care. However, the date of last normal menses and first date prenatal care began were used to calculate the trimester respondents began prenatal care. This calculation is often used for this purpose (Pennsylvania Department of Health, 2013).

Data Analysis

Statistical Analysis Systems (SAS) (Statistical Analysis Systems) version 9.3 was used to analyze the data . A total of 22 preeclampsia cases were noted in 2007 and 16 cases in 2008. As a result we had two outcomes preeclampsia only and preeclampsia or eclampsia. Frequencies and percentages were obtained to examine demographic characteristics of respondents and logistic regression analyses were conducted to estimate smoking related preeclampsia/preeclampsia or eclampsia risk. Four models were used for the logistic regression analyses. Model 1 yielded crude odds ratio (OR) and model 2 the age adjusted OR. Model 3 was a multivariate model, controlling for maternal age, maternal ethnicity, trimester prenatal care began, WIC enrollment and insurance status. Model 4 included confounders in model 3 and maternal pre-pregnancy BMI. To observe the effects of WIC enrollment and prenatal care on smoking related preeclampsia risk we used age adjusted models. These analyses were conducted separately for 2007 and 2008.

RESULTS

Tables 1 and 2 present demographic characteristics, as well as frequency and percentages for the smoking status of our study population. During 2007, there were 32 488 deliveries in San Bernardino County, 2.12% were affected by preeclampsia and 1.01% of the 32 035 deliveries in 2008 were affected by preeclampsia. The proportion of preeclampsia was highest among 18-39 year old women, Hispanic women, and women who completed high school (12 years of education). In 2007, 2.19% of the deliveries were affected by either preeclampsia or eclampsia. While 2.10% were affected by preeclampsia or eclampsia in 2008. In 2007 and 2008 among women diagnosed with preeclampsia 91% and 93% never smoked, respectively. Preeclampsia or eclampsia

cases were between the ages of 18 and 35 years old, Hispanic, had 12 years of education and used Medi-Cal as primary source of payment for prenatal care.

Table 1. Demographic characteristics and smoking status of mothers with preeclampsia versus mothers with no preeclampsia in San Bernardino County in 2007 and 2008

	2007			2008		
n (%)	Total	No Preeclampsia	Preeclampsia	Total	No Preeclampsia	Preeclampsia
Occurrence	33193	32488 (97.88)	705 (2.12)	32035	31379 (97.95)	656 (1.01)
Maternal Tobacco Use						
Never Smoker	31050	30410 (93.85)	640 (91.04)	29989	29386 (93.76)	603 (92.63)
Smoking During Pregnancy	1430	1388 (4.28)	42 (5.97)	1355	1324 (4.22)	31 (4.76)
Quit at Pregnancy Recognition	626	605 (1.87)	21 (2.99)	38	631 (2.01)	17 (2.61)
Maternal Age						
< 18 Years	1422	1391 (4.28)	31 (4.40)	1317	1293(4.12)	24 (3.66)
18-<35 Years	27918	27376 (84.27)	542 (76.88)	26886	26373 (84.05)	513 (78.20)
35 Years or older	3851	3719 (11.45)	132 (18.72)	3832	3713 (11.83)	119 (18.14)
Mother's Race/Ethnicity						
Hispanic	20059	19664 (60.04)	395 (56.03)	19213	18840 (60.04)	373 (56.86)
Non-Hispanic white	8218	8028 (24.71)	190 (26.95)	8013	7837 (24.98)	176 (26.83)
Non-Hispanic black	2800	2712 (8.35)	88 (12.48)	2756	2685 (8.56)	71 (10.82)
Asian/Pacific Islander	1925	1897 (5.84)	28 (3.97)	1824	1796 (5.72)	28 (4.27)
Other/Multi/Unknown	191	187 (0.58)	4 (0.57)	229	221 (0.70)	8 (1.22)
Mother's Years of Education						
0-8 Years	2360	2311 (7.17)	49 (6.98)	2045	2010 (6.46)	35 (5.39)
9-11 Years	7831	7706 (23.91)	125 (17.81)	7504	7357 (23.66)	147 (22.65)
12 Years	11145	10886 (33.77)	259 (36.89)	10399	10173 (32.71)	226 (34.82)
13-15 Years	7445	7254 (22.51)	191 (27.21)	7699	7534 (24.23)	165 (25.42)
16 Years or More	4153	4075 (12.64)	78 (11.11)	4102	4026 (12.95)	76 (11.71)
Principal Source of Payment for Prenatal Care						
Uninsured	1084	1061 (3.27)	23 (3.26)	888	871 (2.78)	17 (2.59)
Private Insurance	13920	13684 (42.12)	236 (33.48)	13295	13078 (41.68)	217 (33.08)
Medi-Cal	16236	15863 (48.83)	373 (52.91)	15844	15486 (49.35)	358 (54.57)
Other	1953	1880 (5.79)	73 (10.35)	2008	1944 (6.20)	64 (9.76)

Table 2. Demographic characteristics and smoking status of mothers with preeclampsia or eclampsia in San Bernardino County in 2007 and 2008

	2007			2008		
n (column %)	Total	No Preeclampsia or Eclampsia	Combined Preeclampsia or Eclampsia	Total	No Preeclampsia or Eclampsia	Combined Preeclampsia or Eclampsia
Occurrence	33193	32466 (97.81)	727 (2.19)	32035	31363 (97.90)	672 (2.10)
Maternal Tobacco Use						
Never Smoker	31050	30393 (93.86)	657 (90.62)	29989	29371 (93.76)	618 (92.65)
Smoking During Pregnancy	1430	1386 (4.28)	44 (6.07)	1355	1324 (4.23)	31 (4.65)
Quit at Pregnancy Recognition	626	602 (1.86)	24 (3.31)	648	630 (2.01)	18 (2.70)
Maternal Age						
< 18 Years	1422	1390 (4.28)	32 (4.40)	1317	1293 (4.12)	24 (3.57)
18-<35 Years	27918	27357 (84.27)	561 (77.17)	26886	26360 (84.05)	526 (78.27)
35 Years or older	3851	3717 (11.45)	134 (18.43)	3832	3710 (11.83)	122 (18.15)
Mother's Race/Ethnicity						
Hispanic	20059	19655 (59.21)	404 (55.57)	19213	18830 (60.04)	383 (56.99)
Non-Hispanic white	8218	8022 (24.71)	196 (26.96)	8013	7836 (24.98)	177 (26.34)
Non-Hispanic black	2800	2706 (8.33)	94 (12.93)	2756	2682 (8.35)	74 (11.01)
Asian/Pacific Islander	1925	1897 (5.84)	28 (3.85)	1824	1794 (5.72)	30 (4.46)
Other/Multi/Unknown	191	186 (0.57)	5 (0.69)	229	221 (0.70)	8 (1.19)
Mother's Years of Education						
0-8 Years	2360	2309 (7.17)	51 (7.04)	2045	2009 (6.46)	36 (5.41)
9-11 Years	7831	7699 ((23.90)	132 (18.23)	7504	7352 (23.65)	152 (22.86)
12 Years	11145	10877 (33.77)	268 (37.02)	10399	10169 (32.71)	230 (34.59)
13-15 Years	7445	7251 (22.51)	194 (26.60)	7699	7529 (24.22)	170 (25.56)
16 Years or More	4153	4074 (12.65)	79 (10.91)	4102	4025 (12.95)	77 (11.58)
Principal Source of Payment for Prenatal Care						
Uninsured	1084	1060 (3.26)	24 (3.30)	888	871 (2.78)	17 (2.53)
Private Insurance	13920	13676 (42.12)	244 (33.56)	13295	13705 (41.69)	220 (32.74)
Medi-Cal	16236	15851 (48.82)	385 (52.96)	15844	15473 (49.34)	371 (55.21)
Other	1953	1879 (5.79)	74 (10.18)	2008	1944 (6.20)	64 (9.52)

Tables 3 and 4 present crude, age adjusted and multivariate odds ratios for preeclampsia risk. Significant results were noted for our crude and age adjusted models. During 2007 women who never smoked were 31% [95% CI: 0.50,0.94] less likely to develop preeclampsia compared to those who smoked during pregnancy. For our preeclampsia or eclampsia outcome women who never smoked had an age adjusted odds ratio of 0.67 [95% CI: 0.49,0.92]. No significant findings were noted in our multivariable models. An association was noted between never smoked and preeclampsia during 2007 when adding WIC and early prenatal care separately to the age

adjusted models. When accounting for the effects WIC enrollment women who never smoked had age adjusted odds ratio 0.68 [95%CI: 0.49,0.93] and 0.66 [95%CI: 0.49,0.90] for preeclampsia and preeclampsia or eclampsia respectively during 2007 compared to those who smoked during pregnancy. Similar results were noted when accounting for the effects of early prenatal care. During 2007 women who never smoked had an age adjusted odds ratio of 0.64 [95%CI: 0.50, 0.94] for preeclampsia and 0.68 [95% CI: 0.49, 0.93] for preeclampsia or eclampsia compared to those who smoked during pregnancy.

Table 3. Crude, Age-adjusted, and Multivariable1 odds ratios with 95% CI for preeclampsia outcomes among mothers in San Bernardino County in 2007 and 2008

	2007			2008		
	Crude	Age-Adjusted	Multivariable	Crude	Age-Adjusted	Multivariable
Maternal Tobacco Use						
Never Smoker	**0.70 (0.51, 0.96)**	**0.69 (0.50, 0.94)**	0.83 (0.59, 1.16)	0.88 (0.61, 1.26)	0.870 (0.604, 1.254)	1.063 (0.724, 1.560)
Smoking During Pregnancy	1.00 (Reference)			1.00 (reference)		
Quit at Smoking Recognition	1.15 (0.67, 1.95)	1.618 (0.70, 2.02)	1.24 (0.77, 2.12)	1.15 (0.63, 2.10)	1.18 (0.65, 2.14)	1.28 (0.70, 2.34)

Multivariable - Adjusted for age, race/ethnicity, WIC utilization, insurance status, and month prenatal care began. CI= Confidence Interval

Table 4. Crude, Age-adjusted, and Multivariable odds ratios with 95% CI for preeclampsia or eclampsia outcomes among mothers in San Bernardino County in 2007 and 2008

	2007			2008		
	Crude	Age-Adjusted	Multivariable	Crude	Age-Adjusted	Multivariable
Maternal Tobacco Use						
Never Smoker	**0.68 (0.50, 0.93)**	**0.67 (0.49, 0.92)**	0.82 (0.59, 1.14)	0.90 (0.62, 1.29)	0.89 (0.62, 1.29)	1.09 1.60)
Smoking During Pregnancy	1.00 (Reference)			1.00 (Reference)		
Quit at Smoking Recognition	1.26 (0.76, 2.08)	1.30 (0.780, 2.150)	1.37 (0.82, 2.28)	1.22 (0.68, 2.20)	1.25 (0.692, 2.245)	1.36 (0.75, 2.48)

Multivariable- Adjusted for age, race/ethnicity, WIC utilization, insurance status, and month prenatal care began. CI= Confidence Interval

DISCUSSION AND CONCLUSION

Researchers examining the relationship between smoking and preeclampsia risk have indicated that smoking is protective against developing preeclampsia (10). This study used smoking during pregnancy as the reference category while previous researchers have used non-smoker as the referent category making it difficult for us to compare our results with these studies (17). Results from this present study indicates that women who never smoked experienced a decreased odds of developing preeclampsia compared to those who smoked during pregnancy when considering age adjusted model. In a similar study exploring the effect of smoking and exposure to household smoking researchers did not find that smoking was protective against preeclampsia (18). Our multivariable models did not yield significant results, indicating that smoking during pregnancy in these samples is associated with many socioeconomic status indicators which were not controlled for in this study such as low socioeconomic status, alcohol use and drug abuse. The study is one of few known studies using women who smoked as a reference category to examine the association between maternal cigarette smoking and preeclampsia. We partly confirmed that non-smokers experience a decreased likelihood of preeclampsia when compared to women who smoked during pregnancy.

This study is not without limitations. In regards to smoking status, smoking status was based on maternal self report and we could not confirm smoking status. Smoking status may have been underreported since it is less socially acceptable to smoke during pregnancy and reporting tends to vary by demographic characteristics (19). Our smoking status classification may have introduced error since there was no actual choice for "never smoked" on the birth certificate and we classified those who indicated "0" as the

average number of cigarettes smoked or the packs of cigarettes smoked for the question asking about cigarette use before and during pregnancy as a "never smoker". We were unable to account for those who smoked but quit longer than 3 months before pregnancy as well as for those who quit but relapsed later in their pregnancy. Information regarding exposure to second/third hand smoke, illicit drug, and alcohol use were not captured on the birth certificate therefore we could not add these variables to our multivariate models. Maternal smoking status at middle or late pregnancy rather than early pregnancy appears to be most important in determining preeclampsia related smoking risk (9). We could not examine this relationship since we did not have cessation and relapse history of the respondent.

Future research should explore the mechanisms regarding why nonsmokers may experience decreased odds of preeclampsia compared to those who smoked during pregnancy. Areas for future research include exploring preeclampsia risk based on smoking habits during various stages of pregnancy, cessation and relapse patterns and exposure to second hand smoke.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

A. Summary and Findings

The results of this study have confirmed the findings from previous research regarding maternal weight status and preeclampsia risk. Women who were overweight or obese based on their pre-pregnancy BMI were noted to have increased odds for preeclampsia compared to those with normal pre-pregnancy BMI. Women who were underweight experienced a decreased odds compared to those with normal pre-pregnancy BMI. The study also confirmed that women who gained more weight during their pregnancy per the Institute of Medicine had higher odds for preeclampsia than those who gained the recommended amount of weight. An inverse relationship was noted between those who gained too little weight and preeclampsia risk compared to those who gained the recommended amount of weight. Similar findings were noted when accounting for the effects of respondent enrollment in WIC and the trimester in which prenatal care began.

Findings regarding maternal smoking related risk were contrary to the body of existing research which suggests that smoking during pregnancy is protective against the development of preeclampsia. Our study found that women who never smoked had experienced a reduction in preeclampsia compared to those who smoked during pregnancy in the age adjusted analyses but not in the multivariate analyses. Similar results were noted when accounting for the effects of WIC enrollment and the trimester in which prenatal care began.

B. Limitations

This study demonstrated the strong association between excess maternal body weight and preeclampsia. This is the only known study to examine WIC and prenatal care enrollment as possible moderators for preeclampsia related to pre-pregnancy BMI, IOM recommendations and maternal cigarette smoking status. The WIC program and prenatal care remain important services for the primary prevention of adverse pregnancy and infant outcomes.

This study was not without limitations. Separate analyses could not be conducted for eclampsia cases there were only 38 cases in 2007 and 2008. Utilizing archival data proved challenging since additional information not collected on the standard U.S. birth certificate could have been used, if collected, to strengthen the study. Information not collected included: (a) trimester respondent enrolled in WIC, (b) food records to assess nutrition status and diet quality, (c) number of times respondents received weight management or smoking cessation counseling, (d) type of weight management or smoking cessation counseling received, (e) exposure to second/third hand smoke, (f) smoking cessation and relapse history before and during pregnancy, and (g) maternal history of alcohol or illicit drug use. Weight and smoking history were self reported and could not be verified. The effects of WIC and prenatal care did not change the odds of preeclampsia occurrence compared to the odds noted when accounting for these variables, indicating that perhaps the measures used to assess these variables may not have been ideal.

C. Areas for Future Research

This study serves to generate hypotheses regarding preeclampsia occurrence. There is still a need to explore primary prevention interventions such as weight management for the reduction of preeclampsia occurrence. Particularly, further investigation is needed to elucidate how enrollment in the WIC program and preconception/prenatal care may reduce preeclampsia occurrence. Additional studies are needed to investigate the association between smoking and preeclampsia, with an emphasis on smoking cessation throughout various stages of pregnancy.

D. Implications for Preventive Care

The modifiable risk factors associated with the occurrence of preeclampsia such as excess body fat and poor nutrition status are issues Preventive Care Specialists encounter in clinical practice. This study suggests that preventive care practice in the area of maternal and child health may prove to be beneficial in reducing maternal and infant mortality and morbidity related to lifestyle factors such as overweight and obesity.

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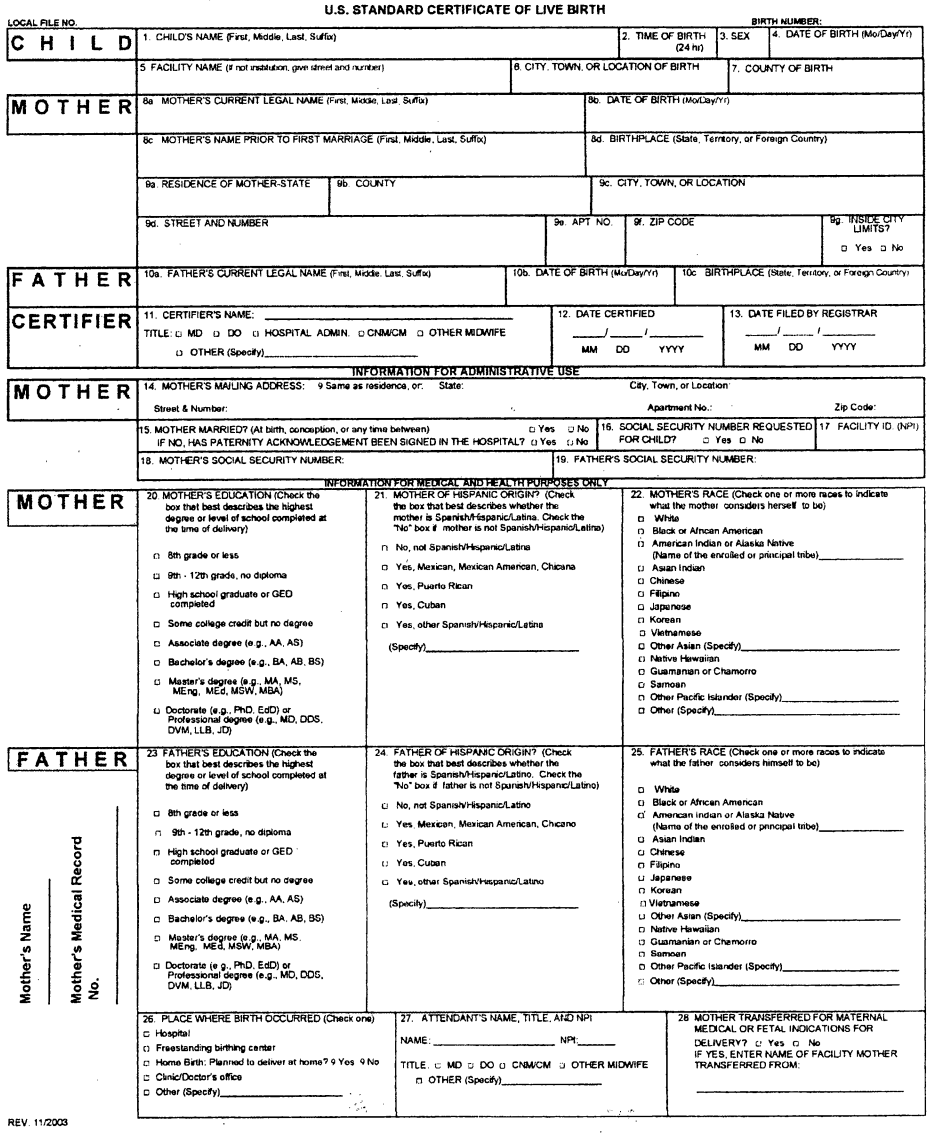
APPENDIX A

Standard United States Birth Certificate



U.S. STANDARD CERTIFICATE OF LIVE BIRTH

LOCAL FILE NO. BIRTH NUMBER:

CHILD

1. CHILD'S NAME (First, Middle, Last, Suffix) | 2. TIME OF BIRTH (24 hr) | 3. SEX | 4. DATE OF BIRTH (Mo/Day/Yr)

5. FACILITY NAME (If not institution, give street and number) | 6. CITY, TOWN, OR LOCATION OF BIRTH | 7. COUNTY OF BIRTH

MOTHER

8a. MOTHER'S CURRENT LEGAL NAME (First, Middle, Last, Suffix) | 8b. DATE OF BIRTH (Mo/Day/Yr)

8c. MOTHER'S NAME PRIOR TO FIRST MARRIAGE (First, Middle, Last, Suffix) | 8d. BIRTHPLACE (State, Territory, or Foreign Country)

9a. RESIDENCE OF MOTHER-STATE | 9b. COUNTY | 9c. CITY, TOWN, OR LOCATION

9d. STREET AND NUMBER | 9e. APT. NO. | 9f. ZIP CODE | 9g. INSIDE CITY LIMITS? ☐ Yes ☐ No

FATHER

10a. FATHER'S CURRENT LEGAL NAME (First, Middle, Last, Suffix) | 10b. DATE OF BIRTH (Mo/Day/Yr) | 10c. BIRTHPLACE (State, Territory, or Foreign Country)

CERTIFIER

11. CERTIFIER'S NAME: _____
TITLE: ☐ MD ☐ DO ☐ HOSPITAL ADMIN. ☐ CNM/CM ☐ OTHER MIDWIFE
☐ OTHER (Specify)_____

12. DATE CERTIFIED ____/____/____ MM DD YYYY

13. DATE FILED BY REGISTRAR ____/____/____ MM DD YYYY

INFORMATION FOR ADMINISTRATIVE USE

MOTHER

14. MOTHER'S MAILING ADDRESS: 9 Same as residence, or: State: City, Town, or Location
Street & Number: Apartment No.: Zip Code:

15. MOTHER MARRIED? (At birth, conception, or any time between) ☐ Yes ☐ No
IF NO, HAS PATERNITY ACKNOWLEDGEMENT BEEN SIGNED IN THE HOSPITAL? ☐ Yes ☐ No

16. SOCIAL SECURITY NUMBER REQUESTED FOR CHILD? ☐ Yes ☐ No

17. FACILITY ID. (NPI)

18. MOTHER'S SOCIAL SECURITY NUMBER:

19. FATHER'S SOCIAL SECURITY NUMBER:

INFORMATION FOR MEDICAL AND HEALTH PURPOSES ONLY

MOTHER

20. MOTHER'S EDUCATION (Check the box that best describes the highest degree or level of school completed at the time of delivery)
☐ 8th grade or less
☐ 9th - 12th grade, no diploma
☐ High school graduate or GED completed
☐ Some college credit but no degree
☐ Associate degree (e.g., AA, AS)
☐ Bachelor's degree (e.g., BA, AB, BS)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)
☐ Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)

21. MOTHER OF HISPANIC ORIGIN? (Check the box that best describes whether the mother is Spanish/Hispanic/Latina. Check the "No" box if mother is not Spanish/Hispanic/Latina)
☐ No, not Spanish/Hispanic/Latina
☐ Yes, Mexican, Mexican American, Chicana
☐ Yes, Puerto Rican
☐ Yes, Cuban
☐ Yes, other Spanish/Hispanic/Latina
(Specify)_____

22. MOTHER'S RACE (Check one or more races to indicate what the mother considers herself to be)
☐ White
☐ Black or African American
☐ American Indian or Alaska Native (Name of the enrolled or principal tribe)_____
☐ Asian Indian
☐ Chinese
☐ Filipino
☐ Japanese
☐ Korean
☐ Vietnamese
☐ Other Asian (Specify)_____
☐ Native Hawaiian
☐ Guamanian or Chamorro
☐ Samoan
☐ Other Pacific Islander (Specify)_____
☐ Other (Specify)_____

FATHER

23. FATHER'S EDUCATION (Check the box that best describes the highest degree or level of school completed at the time of delivery)
☐ 8th grade or less
☐ 9th - 12th grade, no diploma
☐ High school graduate or GED completed
☐ Some college credit but no degree
☐ Associate degree (e.g., AA, AS)
☐ Bachelor's degree (e.g., BA, AB, BS)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)
☐ Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)

24. FATHER OF HISPANIC ORIGIN? (Check the box that best describes whether the father is Spanish/Hispanic/Latino. Check the "No" box if father is not Spanish/Hispanic/Latino)
☐ No, not Spanish/Hispanic/Latino
☐ Yes, Mexican, Mexican American, Chicano
☐ Yes, Puerto Rican
☐ Yes, Cuban
☐ Yes, other Spanish/Hispanic/Latino
(Specify)_____

25. FATHER'S RACE (Check one or more races to indicate what the father considers himself to be)
☐ White
☐ Black or African American
☐ American Indian or Alaska Native (Name of the enrolled or principal tribe)_____
☐ Asian Indian
☐ Chinese
☐ Filipino
☐ Japanese
☐ Korean
☐ Vietnamese
☐ Other Asian (Specify)_____
☐ Native Hawaiian
☐ Guamanian or Chamorro
☐ Samoan
☐ Other Pacific Islander (Specify)_____
☐ Other (Specify)_____

Mother's Name | Mother's Medical Record No.

26. PLACE WHERE BIRTH OCCURRED (Check one)
☐ Hospital
☐ Freestanding birthing center
☐ Home Birth: Planned to deliver at home? 9 Yes 9 No
☐ Clinic/Doctor's office
☐ Other (Specify)_____

27. ATTENDANT'S NAME, TITLE, AND NPI
NAME: _____ NPI:_____
TITLE: ☐ MD ☐ DO ☐ CNM/CM ☐ OTHER MIDWIFE
☐ OTHER (Specify)_____

28. MOTHER TRANSFERRED FOR MATERNAL MEDICAL OR FETAL INDICATIONS FOR DELIVERY? ☐ Yes ☐ No
IF YES, ENTER NAME OF FACILITY MOTHER TRANSFERRED FROM:
_____

REV. 11/2003

MOTHER

29a. DATE OF FIRST PRENATAL CARE VISIT
____/____/____ ☐ No Prenatal Care
MM DD YYYY

29b DATE OF LAST PRENATAL CARE VISIT
____/____/____
MM DD YYYY

30. TOTAL NUMBER OF PRENATAL VISITS FOR THIS PREGNANCY
_____ (If none, enter 00)

31. MOTHER'S HEIGHT
_____ (feet/inches)

32. MOTHER'S PREPREGNANCY WEIGHT
_____ (pounds)

33. MOTHER'S WEIGHT AT DELIVERY
_____ (pounds)

34. DID MOTHER GET WIC FOOD FOR HERSELF DURING THIS PREGNANCY? ☐ Yes ☐ No

35. NUMBER OF PREVIOUS LIVE BIRTHS (Do not include this child)

35a. Now Living
Number ____
☐ None

35b. Now Dead
Number ____
☐ None

36. NUMBER OF OTHER PREGNANCY OUTCOMES (spontaneous or induced losses or ectopic pregnancies)

36a. Other Outcomes
Number ____
☐ None

37. CIGARETTE SMOKING BEFORE AND DURING PREGNANCY
For each time period, enter either the number of cigarettes or the number of packs of cigarettes smoked. IF NONE, ENTER 00.

Average number of cigarettes or packs of cigarettes smoked per day.

	# of cigarettes		# of packs
Three Months Before Pregnancy	_____	OR	_____
First Three Months of Pregnancy	_____	OR	_____
Second Three Months of Pregnancy	_____	OR	_____
Third Trimester of Pregnancy	_____	OR	_____

38. PRINCIPAL SOURCE OF PAYMENT FOR THIS DELIVERY
☐ Private Insurance
☐ Medicaid
☐ Self-pay
☐ Other
(Specify) _____

35c DATE OF LAST LIVE BIRTH
____/____
MM YYYY

36b. DATE OF LAST OTHER PREGNANCY OUTCOME
____/____
MM YYYY

39. DATE LAST NORMAL MENSES BEGAN
____/____/____
MM DD YYYY

40. MOTHER'S MEDICAL RECORD NUMBER

MEDICAL AND HEALTH INFORMATION

41. RISK FACTORS IN THIS PREGNANCY (Check all that apply)

Diabetes
☐ Prepregnancy (Diagnosis prior to this pregnancy)
☐ Gestational (Diagnosis in this pregnancy)

Hypertension
☐ Prepregnancy (Chronic)
☐ Gestational (PIH, preeclampsia)
☐ Eclampsia

☐ Previous preterm birth

☐ Other previous poor pregnancy outcome (Includes perinatal death, small-for-gestational age/intrauterine growth restricted birth)

☐ Pregnancy resulted from infertility treatment-If yes, check all that apply:
☐ Fertility-enhancing drugs, Artificial insemination or Intrauterine insemination
☐ Assisted reproductive technology (e.g., in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT))

☐ Mother had a previous cesarean delivery
If yes, how many _____

☐ None of the above

42. INFECTIONS PRESENT AND/OR TREATED DURING THIS PREGNANCY (Check all that apply)

☐ Gonorrhea
☐ Syphilis
☐ Chlamydia
☐ Hepatitis B
☐ Hepatitis C
☐ None of the above

43. OBSTETRIC PROCEDURES (Check all that apply)

☐ Cervical cerclage
☐ Tocolysis

External cephalic version:
☐ Successful
☐ Failed

☐ None of the above

44. ONSET OF LABOR (Check all that apply)

☐ Premature Rupture of the Membranes (prolonged, ≥12 hrs.)
☐ Precipitous Labor (<3 hrs.)
☐ Prolonged Labor (≥20 hrs.)
☐ None of the above

45. CHARACTERISTICS OF LABOR AND DELIVERY (Check all that apply)

☐ Induction of labor
☐ Augmentation of labor
☐ Non-vertex presentation
☐ Steroids (glucocorticoids) for fetal lung maturation received by the mother prior to delivery
☐ Antibiotics received by the mother during labor
☐ Clinical chorioamnionitis diagnosed during labor or maternal temperature ≥38°C (100.4°F)
☐ Moderate/heavy meconium staining of the amniotic fluid
☐ Fetal intolerance of labor such that one or more of the following actions was taken: in-utero resuscitative measures, further fetal assessment, or operative delivery
☐ Epidural or spinal anesthesia during labor
☐ None of the above

46. METHOD OF DELIVERY

A. Was delivery with forceps attempted but unsuccessful?
☐ Yes ☐ No

B. Was delivery with vacuum extraction attempted but unsuccessful?
☐ Yes ☐ No

C. Fetal presentation at birth
☐ Cephalic
☐ Breech
☐ Other

D. Final route and method of delivery (Check one)
☐ Vaginal/Spontaneous
☐ Vaginal/Forceps
☐ Vaginal/Vacuum
☐ Cesarean
If cesarean, was a trial of labor attempted?
☐ Yes
☐ No

47. MATERNAL MORBIDITY (Check all that apply) (Complications associated with labor and delivery)
☐ Maternal transfusion
☐ Third or fourth degree perineal laceration
☐ Ruptured uterus
☐ Unplanned hysterectomy
☐ Admission to intensive care unit
☐ Unplanned operating room procedure following delivery
☐ None of the above

NEWBORN

NEWBORN INFORMATION

48. NEWBORN MEDICAL RECORD NUMBER

49. BIRTHWEIGHT (grams preferred, specify unit)
_____
9 grams 9 lb/oz

50. OBSTETRIC ESTIMATE OF GESTATION:
_____ (completed weeks)

51. APGAR SCORE:
Score at 5 minutes: _____
If 5 minute score is less than 6,
Score at 10 minutes: _____

52. PLURALITY - Single, Twin, Triplet, etc.
(Specify)_____

53. IF NOT SINGLE BIRTH - Born First, Second, Third, etc. (Specify) _____

54. ABNORMAL CONDITIONS OF THE NEWBORN (Check all that apply)

☐ Assisted ventilation required immediately following delivery
☐ Assisted ventilation required for more than six hours
☐ NICU admission
☐ Newborn given surfactant replacement therapy
☐ Antibiotics received by the newborn for suspected neonatal sepsis
☐ Seizure or serious neurologic dysfunction
☐ Significant birth injury (skeletal fracture(s), peripheral nerve injury, and/or soft tissue/solid organ hemorrhage which requires intervention)
9 None of the above

55. CONGENITAL ANOMALIES OF THE NEWBORN (Check all that apply)

☐ Anencephaly
☐ Meningomyelocele/Spina bifida
☐ Cyanotic congenital heart disease
☐ Congenital diaphragmatic hernia
☐ Omphalocele
☐ Gastroschisis
☐ Limb reduction defect (excluding congenital amputation and dwarfing syndromes)
☐ Cleft Lip with or without Cleft Palate
☐ Cleft Palate alone
☐ Down Syndrome
☐ Karyotype confirmed
☐ Karyotype pending
☐ Suspected chromosomal disorder
☐ Karyotype confirmed
☐ Karyotype pending
☐ Hypospadias
☐ None of the anomalies listed above

56. WAS INFANT TRANSFERRED WITHIN 24 HOURS OF DELIVERY? 9 Yes 9 No
IF YES, NAME OF FACILITY INFANT TRANSFERRED
TO:_____

57. IS INFANT LIVING AT TIME OF REPORT?
☐ Yes ☐ No ☐ Infant transferred, status unknown

58. IS THE INFANT BEING BREASTFED AT DISCHARGE?
☐ Yes ☐ No

Mother's Name _____ Mother's Medical Record No. _____

APPENDIX B

Documentation of IRB Approval

LOMA LINDA UNIVERSITY
ADVENTIST HEALTH
SCIENCES CENTER

INSTITUTIONAL REVIEW BOARD

RESEARCH PROTECTION PROGRAMS
24887 Taylor Street • Suite 202 • Loma Linda, CA 92350
(909) 558-4531 (voice) • (909) 558-0131 (fax)

Exempt Notice ***IRB# 5130020***

To: **Modeste, Naomi N**

Department: **Health Promotion & Education**

Protocol: **Maternal smoking body mass index and preeclampsia and eclampsia risk among women living in San Bernardino county**

Your application for the research protocol indicated above was reviewed administratively on behalf of the IRB. This protocol is determined to be exempt from IRB approval as outlined in federal regulations for protection of human subjects, 45 CFR Part 46.101(b)(4).

Stipulations of approval:

Please note the PI's name and the IRB number assigned to this IRB protocol (as indicated above) on any future communications with the IRB. Direct all communications to the IRB c/o Research Protection Programs.

Although this protocol is exempt from further IRB review as submitted, it is understood that all research conducted under the auspices of Loma Linda University will be guided by the highest standards of ethical conduct.

Signature of IRB Chair/Designee: R L Rigsby MD Date: 1/28/13

IRB Chair:
Rhodes L. Rigsby, M.D.
Department of Medicine
(909) 558-2341, rrigsby@llu.edu

IRB Administrator:
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