Does Gestational Diabetes Mellitus Increases the Risk of Preeclampsia Among Primigravid Women?

by

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ABSTRACT

Gestational diabetes mellitus (GDM) and preeclampsia are serious complications of pregnancy which are associated with both short- and long-term adverse health outcomes for the mother as well as the fetus. The increase in prevalence of these conditions has become a major public health concern. The purpose of this study is to examine the association and risk imposed by GDM for preeclampsia in primigravid women. This descriptive study was conducted using data retrieved from the electronic medical records of a large integrated health system in Florida. The data for this analysis included pregnancy records for patients at least 18 years of age over a six-year period from 2011 – 2016. The study was limited to primigravida women with a singleton pregnancy. The risk of preeclampsia for GDM positive women was compared to non-GDM positive women. Chi-square tests and multivariable logistic regression models were performed to conduct the analysis. In this study, the prevalence of preeclampsia was slightly higher among GDM positive women around 9.1% compared to 7.4% in non-GDM positive women. Although the results did not reach statistical significance, the risk of preeclampsia was higher among women with GDM compared to women without GDM (AOR=1.33; 95% CI 0.9,2.1; p =0.1826). Therefore, it is necessary to develop programs and interventions with preventive efforts to reduce the rates of GDM and preeclampsia at patient and provider level.

CHAPTER ONE: INTRODUCTION

Gestational diabetes mellitus (GDM) and preeclampsia are the most common conditions causing complications during pregnancy worldwide, and their concurrence impacts the perinatal outcomes for mother and fetus (Schneider, Freerksen, Röhrig, Hoeft, & Maul, 2012; X. Zhang & Xiao, 2019). These conditions occur during pregnancy and the clinical symptoms resolve after delivery.

GDM is defined as glucose or carbohydrate intolerance recognized for the first time during pregnancy in women who never had diabetes (American Diabetes, 2013; DeSisto, Kim, & Sharma, 2014). It has become one of the major health problems worldwide and since the past decade, it has significantly escalated the global health care burden (Chen et al., 2009; Ma, Chan, Tam, Hanson, & Gluckman, 2013). GDM increases with advanced maternal age and maternal obesity-linked with the increase in sedentary and industrial lifestyle and urbanization across the globe (Erem, Kuzu, Deger, & Can, 2015; Kampmann et al., 2015; Larrabure-Torrealva et al., 2018; Lavery, Friedman, Keyes, Wright, & Ananth, 2017; Ma et al., 2013; Veeraswamy, Vijayam, Gupta, & Kapur, 2012). Literature suggests, diagnosis of GDM increases the probability of having preeclampsia, cesarean sections and operative vaginal deliveries, post-partum hemorrhages and infections, preterm birth, fetal macrosomia, congenital anomalies, neonatal hypoglycemia, and shoulder dystocia (Boriboonhirunsarn & Waiyanikorn, 2016; Erem et al., 2015; Kampmann et al., 2015; X. Zhang & Xiao, 2019). Furthermore, the rate of stillbirths

is higher among women with GDM, compared to unaffected women (Erem et al., 2015; Kampmann et al., 2015).

Preeclampsia is a multisystem disorder characterized by new-onset hypertension (high blood pressure) and proteinuria (excess protein in urine) after 20 weeks of gestation in a woman who was previously normotensive (Ghulmiyyah & Sibai, 2012; Gupte & Wagh, 2014; Lee et al., 2017). Preeclampsia is classified into mild and severe; preeclampsia is considered mild when blood pressure greater than 140/90 mmHg systolic/diastolic occurs at or after 20 weeks of gestation and new onset of more than 300 mg of protein detected in maternal urine over a 24 hour period, whereas blood pressure of greater than160 mmHg systolic or 110 mmHg diastolic and new onset of proteinuria more than 5000 mg over a 24 hour period is classified as severe preeclampsia (Ananth, Keyes, & Wapner, 2013; Eiland, Nzerue, & Faulkner, 2012; Gupte & Wagh, 2014; Weissgerber & Mudd, 2015). The incidence of preeclampsia has increased over the past two decades. Preeclampsia is a leading cause of maternal and infant mortality and morbidity worldwide (Eiland et al., 2012; Ghulmiyyah & Sibai, 2012; Roberts & Lain, 2002; Wen et al., 2012). Preeclampsia accounts for proportionately more maternal deaths in developing than in developed countries leading to high maternal morbidity and is associated with an increase in the number of admissions to intensive care units during pregnancy (Ghulmiyyah & Sibai, 2012; Gupte & Wagh, 2014; Roberts & Lain, 2002; Wen et al., 2012). Preeclampsia increases the risk of preterm births and may lead to the future development of renal, cardiovascular and liver disease in the mother (Östlund, Haglund, & Hanson, 2004; Wen et al., 2012; X. Zhang & Xiao, 2019).

Pathophysiology of GDM and Preeclampsia

Our understanding of the pathophysiology of preeclampsia remains elusive. Preeclampsia usually has onset on or after 20 weeks of gestation occurs due to inadequate invasion of placenta leading to placental hypoxia or ischemia (Hubel, 1999; Young, Levine, & Karumanchi, 2010). Phipps, Prasanna, Brima, and Jim (2016) states this placental ischemia is linked to incomplete spiral artery remodeling in the uterus and leads to release of antiangiogenic factors. Other studies also demonstrate placenta releases soluble or antiangiogenic factors like tyrosine kinase and soluble endoglin into maternal plasma which cause systemic maternal endothelial dysfunction resulting in hypertension, proteinuria and other systemic problems of preeclampsia (Eiland et al., 2012; Hubel, 1999; Weissgerber & Mudd, 2015). GDM is detected between 24-28 weeks of gestation and occurs due to the insufficient pancreatic response that fails to compensate for insulin resistance occurring during pregnancy, while preeclampsia is more often a third-trimester phenomenon (Buchanan, Xiang, & Page, 2012; Gilmartin, Ural, & Repke, 2008; Plows, Stanley, Baker, Reynolds, & Vickers, 2018). Literature suggests hyperglycemia (i.e. increase in the level of glucose in the body) induced metabolic syndrome and dyslipidemia are associated with the pathophysiology of both GDM and preeclampsia (Civantos et al., 2019; Lee et al., 2017; X. Zhang & Xiao, 2019). However, in normal pregnancy insulin resistance is a physiologic phenomenon, which in predisposed patients could lead to the development of hyperinsulinemia leading to the development of gestational hypertension, preeclampsia and gestational diabetes mellitus (Mastrogiannis, Spiliopoulos, Mulla, & Homko, 2009).

Prevalence and Trends of GDM and Preeclampsia

GDM is a common condition that precipitates during pregnancy with a worldwide prevalence ranging from 6 – 13% (Larrabure-Torrealva et al., 2018; Zhou et al., 2018).

According to statistics presented by the International Diabetes Federation in 2015, 17.8 million of births were affected by gestational diabetes. According to Centers for Disease Control and Prevention (CDC), approximately 9% of all pregnancies in the United States are complicated by GDM annually (Deputy, Kim, Conrey, & Bullard, 2018; DeSisto et al., 2014; Larrabure-Torrealva et al., 2018; Zhou et al., 2018). The rates seen in different U.S. studies differ depending upon the specific population studied and screening and diagnostic approach used for identification (DeSisto et al., 2014; Erem et al., 2015). Several studies examined the trends of GDM by maternal age, race, socioeconomic status, maternal education level and geographic location in the U.S. (Deputy et al., 2018; Getahun, Nath, Ananth, Chavez, & Smulian, 2008; Zhou et al., 2018). The prevalence of GDM has increased gradually over the past 30 years in the U.S. Getahun et al. (2008), noted an increase in prevalence in GDM from 1.9% in 1990 to 4.2% in 2004. On the other hand, two more recent studies reported that the prevalence of GDM increased from 3.7% to 5.8% from 2000 to 2010 (Deputy et al., 2018) and from 4.6% in 2006 to 8.2% in 2016 (Zhou et al., 2018). The trends of GDM increased from 3.6 to 5.3 per 100 deliveries between 2000 to 2010 in Florida (Bardenheier et al., 2015). The rates of GDM in Florida also vary by race/ethnicity i.e. 8.4% in Asian, 5.6% in Hispanic, 4.9% in non-Hispanic blacks and 4.9% in non-Hispanic whites (Bardenheier et al., 2013, 2015). Furthermore, the 2013 Florida Pregnancy Risk Assessment Monitoring System Data (PRAMS) delineates the prevalence of 9.8 % in gestational diabetes during pregnancy among new mothers residing in Florida.

Preeclampsia affects 5 – 8% of all pregnancies and leads to 50,000 maternal deaths worldwide annually (Jeyabalan, 2013; Wen et al., 2012). Due to inaccessibility to advanced hospital and prenatal care, the rates of preeclampsia are higher in developing nations

(Ghulmiyyah & Sibai, 2012). In the U.S, preeclampsia complicates 3 – 6% of pregnancies, with 1.5 – 2 times greater incidence among first pregnancies (Ananth et al., 2013; U. P. S. T. Force, 2017; Lee et al., 2017). The CDC (2020), states that 1 in 25 pregnancies are affected by preeclampsia in the U.S. Even though the estimates of preeclampsia rates were inconsistent in different studies, an overall upward trend was noted in the rate since 1980 (Ananth et al., 2013; Wallis, Saftlas, Hsia, & Atrash, 2008). Researchers studied secular trends of preeclampsia in the U.S. from 1987 to 2004 and found incidence of preeclampsia increased significantly over the 18 year study period, ranging from 2.5% in 1987 to 3.2% in 2004 (Bardenheier et al., 2015; Wallis et al., 2008). Whereas, in an age-period-cohort study, the overall rates of preeclampsia ranged from 3.4% in 1980 to 3.8% in 2010 (Ananth et al., 2013).

Sociodemographic Disparities of GDM and Preeclampsia in the United States

Researchers examining trends of GDM and preeclampsia over the years have identified differences in the prevalence by race/ethnicity, socio-economic, maternal age and education, parity, body mass index, age period cohort, seasonal variation, and household income (Ananth et al., 2013; Breathett, Muhlestein, Foraker, & Gulati, 2014; DeSisto et al., 2014; Janani & Changaee, 2017; C. Kim et al., 2014; S. Y. Kim et al., 2012; Lawrence, Contreras, Chen, & Sacks, 2008; Pitakkarnkul, Phaloprakarn, Wiriyasirivaj, Manusirivithaya, & Tangjitgamol, 2011; Zhou et al., 2018). Zhou et al. (2018) found that while overall rates of GDM in the U.S. increased from 2006 to 2016 still the pattern in rates are similar over the course of time when studying impact of BMI, maternal age and household income over GDM i.e. higher rates of GDM in women with BMI >30kg/m^2, higher prevalence in women of age group between 25-44 and 45-64 years. Women living in families with household income below 100% federal poverty line (FPL) and between 100-199% FPL had the highest rates of GDM. According to 2015

Florida PRAMS data, higher prevalence of GDM was seen in women who are 35 years or older and had less than high school education. The overall prevalence of GDM is higher among Asian, Pacific Islanders, Hispanic, American Indians /Alaska Natives compared to non-Hispanic Blacks and non-Hispanic White women (Lavery et al., 2017; Ma et al., 2013; Zhou et al., 2018). Another leading factor associated with an increment in prevalence of GDM could be changes made less than 10 years ago in guidelines and recommendations for diagnosing GDM according to Hypoglycemia and Adverse Pregnancy Outcomes (HAPO) criteria reducing the threshold of blood sugar level for pregnant women (Group, 2008, 2009).

Wallis et al. (2008) conducted the secular trend analysis comparing the rates of preeclampsia between 1987 – 1995 and 1996 – 2004 using the National Hospital Discharge Survey (NHDS) data. The authors noted the consistent increase in the rates of preeclampsia in all age groups between 1996 – 2004. They also mentioned the rates were higher in the South and Northeast region compared to Midwest and West regions of the U.S. Ananth et al. (2013), noted the rates of mild preeclampsia reduced from 3% to 2.2% in 1987 to 2010 among women under the age of 30, whereas the rates increased by 1.5% among the age group 35 to 45 years old. In comparison, the rates of severe preeclampsia increased consistently over the course of the study period in all age groups. The authors also mentioned the higher risk of mild preeclampsia in women born in the 1970s whereas the risk of severe preeclampsia was noted in women born in recent decades (Ananth et al., 2013). Researchers studying the seasonal variation in the prevalence of preeclampsia associate the change in rates to environmental factors (Pitakkarnkul et al., 2011; Wallis et al., 2008). Ghosh et al. (2014) noted Hispanic women and Asian/Pacific Islanders as more likely to remain normotensive with lower odds of developing mild preeclampsia compared to non-Hispanic white women. However, non-

Hispanic black women have higher odds of suffering from mild- preeclampsia compared to non-Hispanic white women (Ghosh et al., 2014). Moreover, Breathett et al. (2014) studied the baseline demographic by time period from 1997 to 2006 in the U.S., noting the significant increase in the overall trends among African Americans compared to Caucasians. The authors also noted the mean prevalence of preeclampsia was higher among African Americans (40.1 per 1000 deliveries) compared to Caucasians (28.1 per 1000 deliveries). The changes in the trend of preeclampsia are considered to be impacted by an increased incidence of obesity and modification in the definition and diagnostic criteria of preeclampsia (U. P. S. T. Force, 2017; Ghosh et al., 2014). Furthermore, the presence of these social disparity makes it difficult to access health care, thus making the underprivileged population the most vulnerable group for encountering GDM and preeclampsia. Moreover, these complications have disposed of not only physical, social, mental but also financial burden at each level of the socioecological framework (Deputy et al., 2018; Kampmann et al., 2015).

Associated Risk Factors with GDM and Preeclampsia

Epidemiological evidence suggests an epidemic of obesity in the U.S. and worldwide, and this is considered to be strongest attributable and possibly modifiable risk factor for both GDM and preeclampsia (Erem et al., 2015; Kuklina, Ayala, & Callaghan, 2009; Östlund et al., 2004; Zhou et al., 2018). Chu et al., (2007) described the risk of developing GDM among overweight, obese and severely obese women to be two, four and eight times respectively higher as compared to women with normal weight. GDM case complicated by preeclampsia is directly related to pre-pregnancy weight and interpregnancy weight gain (Wen et al., 2012). Existing literature proposes the presence of common risk factors between GDM and preeclampsia; including advanced maternal age, decreased physical activity, nulliparity, and use of artificial

insemination techniques resulting in increasing the number of multifetal pregnancies (Jeyabalan, 2013; Lee et al., 2017; Östlund et al., 2004; Weissgerber & Mudd, 2015; X. Zhang & Xiao, 2019). Furthermore, GDM is considered a risk factor for the development of preeclampsia (Lee et al., 2017; Östlund et al., 2004).

Risk factors associated with GDM include family history of diabetes, eventful obstetric history or history of GDM in previous pregnancy, history of unexplained miscarriage or stillbirth, insulin resistance and cigarette smoking (Dabelea et al., 2005; Erem et al., 2015; Tobias, Zhang, van Dam, Bowers, & Hu, 2011; Zhou et al., 2018). Although, there is limited literature studying the association of genetic and environmental factors. Few studies observed the impact of perfluorooctanoic acid (PFOA), which disrupts the endocrine system over GDM (C. Zhang, Rawal, & Chong, 2016). Women with polycystic ovarian disease or hypertensive disorder before pregnancy are at an increased risk for developing GDM (Lo et al., 2017). Other factors such as short stature and mother's birth weight have been posited as increasing the risk of GDM but studies remain inconsistent (Innes et al., 2002). Tobias et al. (2011) reported a meta-analysis of five studies estimating the association between physical activity during early pregnancy and GDM and found a 24% risk reduction of GDM in women involved in regular physical activity whereas Dempsey, Butler, and Williams (2005) found that moderate exercise during pregnancy reduces the risk for both GDM and preeclampsia.

Preeclampsia has been found to be associated with a range of risk factors. Nulliparity increased the risk of preeclampsia by threefold (Lin et al., 2015; Weissgerber & Mudd, 2015). Jeyabalan (2013) states this association is due to an immunological mechanism protecting against the paternal antigens in subsequent pregnancies. Other predisposing conditions for preeclampsia include family history of preeclampsia-eclampsia, previous history of

preeclampsia, acute or chronic hypertension, diabetes (type 1 or 2), hyperlipidemia, increased trophoblastic masses due to history of multifetal pregnancies and hydatidiform mole, and cardiovascular disorders (Eiland et al., 2012; Jeyabalan, 2013; Wallis et al., 2008; Weissgerber & Mudd, 2015; Wen et al., 2012). The effects of smoking still remain a controversy, the overall impact of smoking is harmful for both condition (England & Zhang, 2007; Jeyabalan, 2013). Although literature shows the unconventionally beneficial effect of smoking for preeclampsia, smoking is considered to be a risk factor for GDM (Jeyabalan, 2013; Wendland, Duncan, Belizán, Vigo, & Schmidt, 2008).

Adverse Health Effects of GDM and Preeclampsia in Mother and Fetus

Maternal consequences. GDM and preeclampsia are associated with maternal and fetal complications. Maternal hyperglycemia has an immense effect on placental metabolism, growth, and development which causes higher chances of spontaneous abortion, postpartum hemorrhage, and intrauterine growth retardation (Vambergue & Fajardy, 2011; Farrar, Duley, Dowswell & Lawlor, 2017). Women diagnosed with GDM and preeclampsia have a higher risk for cesarean and operative vaginal deliveries, increased risk of developing hemorrhages during the post-partum period and urinary tract infections. Women with history of GDM or preeclampsia are at risk for impaired glucose tolerance and type 2 diabetes mellitus in the course of follow-up and early adulthood (Deputy et al., 2018; Kampmann et al., 2015; Lin et al., 2015; Östlund et al., 2004; Wendland et al., 2008). Erem, et al., states that women diagnosed with GDM have a six times higher risk for developing type 2 diabetes mellitus after pregnancy compared to women without GDM. Women diagnosed with GDM are more likely to give birth to large (birth weight >4500g) babies with congenital anomalies, neonatal hypoglycemia, shoulder dystocia and even

rates of stillbirths are higher among these women (Boriboonhirunsarn & Waiyanikorn, 2016; Erem et al., 2015; Kampmann et al., 2015).

Preeclampsia affects almost all organ systems and an untreated case could result in eclampsia (onset of tonic-clonic seizures) (Jeyabalan, 2013; Weissgerber & Mudd, 2015). Preeclampsia also predisposes women to significant vascular complications such as cardiovascular disorders, stroke and renal or liver failure (Lin et al., 2015; Östlund et al., 2004; Weissgerber & Mudd, 2015; Wendland et al., 2008). Higher incidence of cesarean sections is also seen with both conditions which could also be associated with maternal obesity and cephalon-pelvic disproportion (Boriboonhirunsarn & Waiyanikorn, 2015). Although advancements in medical science have led to better health care to overcome these complications, the consequences of GDM and preeclampsia continue to impact the rates of maternal and infant mortality and morbidity. Moreover, these women and their children are prone to suffer from chronic diseases later in their life. Randomized control trial studies for diet/lifestyle modification and medical treatment have shown the reduction in type 2 DM rates in women with the previous history of GDM (Farahvar, Walfisch, & Sheiner, 2019; Gray et al., 2018; Lo et al., 2017).

Fetal consequences. GDM mothers are at higher risk of developing placentomegaly which leads to decreasing the oxygen supply in the placenta. This impaired supply increases the fetal oxygen demand which leads to an increased level of insulin (hyperinsulinemia) in the fetus (Vambergue & Fajardy, 2011). As fetal growth depends on the placental function, impaired levels of insulin negatively impacts the placenta leading to fetal macrosomia (large size baby). Macrosomia is characterized by increased muscle mass, higher body fat and organomegaly without impacting brain size (D. Mitanchez et al., 2015). Furthermore, antenatal and post-natal mortality and morbidities are significantly higher in GDM cases complicated by preeclampsia

(Lin et al., 2015). Evidence suggests higher rates of stillbirth and intrauterine growth retardation are associated with preeclampsia (Backes et al., 2011; Lin et al., 2015). Infants born to GDM women also suffering from preeclampsia are usually born very low birth weight and preterm, increasing the risk of developing long term neurological and respiratory problems, and suffer from hypoglycemia in the early phase of life (Backes et al., 2011; Lin et al., 2015; Metzger et al., 2007; Mitanchez, Yzydorczyk, & Simeoni, 2015; Weissgerber & Mudd, 2015; Wendland et al., 2008). Maternal hyperglycemia and hyperinsulinism increases the risk of fetus for developing other chronic disease such as type 2 diabetes mellitus, cardiovascular diseases, structural hypothalamic changes, etc. in early stages of life (Backes et al., 2011; Damm et al., 2016; Di Bernardo et al., 2017; Farahvar et al., 2019; Lee et al., 2017; Lin et al., 2015).

Screening and Diagnosis for GDM and Preeclampsia

Early detection of the women at risk for GDM and preeclampsia would allow to alleviate the associated adverse health outcomes and lead to safe completion of pregnancy for mother and child (Kane, 2016; C. Kim et al., 2014).

Healthy People 2020 recommends screening every pregnant woman for GDM at or after 24 weeks of pregnancy. Every woman should have a 1-hour glucose test (glucose challenged test [GCT]) at 24 to 28 weeks of gestation. In GCT, fasting blood sugar is tested and then 50 g of glucose is given to a patient, one hour later blood is taken to evaluate plasma glucose level. The level of more than 130 –140 mg/dl is the indication for undergoing oral glucose tolerance test (OGTT) (Farrar, et al., 2017; Gilmartin, Ural, & Repke, 2008). In 2-hour OGTT, fasting blood sugar is tested, then 75 g of glucose is given to the patient and blood samples are collected at 1 hour and 2 hours. The diagnostic criteria for GDM is fasting glucose levels greater than 95 mg/dl, after 1-hour more than 180 mg/dl, after 2 hours level greater than 155 mg/dl to 199mg/dl

(Koning et al., 2018). In 2010, the International Association of Diabetes and Pregnancies Groups (IADPSG) proposed screening every pregnant woman with single 75-g OGTT. This resulted in an increased prevalence of GDM because it helped identify more cases of GDM (Assaf-Balut et al., 2016). Glycosylated hemoglobin (HbA1c) test measures glycated hemoglobin where hemoglobin in red blood cells naturally bonds with glucose and is a single non- fasting blood test that estimates the level of blood glucose over the past 4 – 8 weeks. Table 1 presents the diagnostic criteria of GDM by different organizations.

The US Preventive Services Task Force (USPSTF) recommends all pregnant women should be screened for preeclampsia throughout pregnancy with blood pressure measurement and urine test for proteinuria at each antenatal visit (U. S. P. S. T. Force et al., 2017). Enhancing routine antenatal investigation, risk factor-based screening, management and early start of prophylactic treatment especially in the first trimester would help early detection and identification of women at high risk for preeclampsia (Duhig, Vandermolen, & Shennan, 2018; Kane, 2016). The effects of a low dose of aspirin during pregnancy to reduce the incidence of preeclampsia still remains a controversy (Atallah et al., 2017). However, a recent study conducted by Haffman and colleague noted the beneficial effects of initiating of low dose aspirin therapy during first trimester of pregnancy reduced the incidence of preterm deliveries before 37 weeks of gestation (Hoffman et al., 2020). Moreover, the USPSTF and UK National Institute of Health and Care Excellence (NICE), recommend giving prophylactic treatment of aspirin to all pregnant women at high risk for preeclampsia and the American College of Obstetricians and Gynecologist Task Force on Hypertension in Pregnancy recommends only providing aspirin to women with a previous history of preeclampsia and at risk for preterm delivery (i.e. <34 weeks of gestation). Duhig et al. (2018) noted the association of low dietary and serum calcium

concentrations with preeclampsia; the World Health Organization recommends daily calcium supplementation of 1.5 – 2 grams especially in the second trimester of pregnancy in women with low dietary intake of calcium. However, there is a lack of uniformity in screening criteria for both approaches and prediction and diagnosis still remain a challenge for health care practitioners.

Association between GDM and Preeclampsia

The epidemiological evidence reported by researchers evaluating the association of GDM and preeclampsia suggests that GDM is an independent risk factor for preeclampsia (Östlund et al., 2004; Schneider et al., 2012; Weissgerber & Mudd, 2015). Evidence-based literature signifies insulin resistance, inflammatory disorders and endothelial dysfunction are commonly present in GDM and preeclampsia (Lee et al., 2017; Östlund et al., 2004; Schneider et al., 2012; Sivakumar, March 2014; Wen et al., 2012; Wendland et al., 2008).

Yogev, Xenakis, and Langer (2004) conducted a retrospective analysis of 1,813 women diagnosed with gestational diabetes between 1993-1999 and reported approximately 9.6% of the cases of GDM were complicated by preeclampsia. These results align with the study conducted in Sweden by Ostlund and colleagues in over 430,852 women, out of which 3,448 had GDM and 12,005 had preeclampsia. Authors noted a higher rate of preeclampsia i.e. 6.1 % in GDM women compared to 2.8% in non-GDM women (Östlund et al., 2004). Another study conducted in Germany found the overall prevalence of both the disease together was around 4.1% out of the population of 647,385 (Schneider et al., 2012).

Even though existing literature shows that both conditions share some common risk factors, including advanced maternal age, higher pre-pregnancy BMI, nulliparity and multifetal pregnancy, their co-occurrence may lead to worsening of pregnancy outcomes (Larrabure-

Torrealva et al., 2018; Lowe et al., 2019; Östlund et al., 2004; Schneider et al., 2012; Wen et al., 2012; Wendland et al., 2008; X. Zhang & Xiao, 2019). Still, there is a dearth in literature exploring the association between GDM and preeclampsia.

Scope of the Study

GDM and preeclampsia are serious complications of pregnancy which are associated with both short- and long-term adverse health outcomes for the mother as well as the fetus. With the increase in the prevalence of both GDM and preeclampsia and associated adverse health effects, the prospects of the future are alarming. Moreover, there is a scarcity of research exploring the association between these conditions. Thus, this thesis aims to develop a better understanding of the associated risk factors for preeclampsia and explore to what extent the diagnosis of GDM increases the risk of preeclampsia in primigravid women.

Table 1: Diagnostic Criteria of GDM

Organization	Oral Glucose Tolerance Test load	Plasma glucose mg/dl			
		Fasting	1-hour	2-hour	3- hour
World Health Organization*	75 g	95	180	153	-
American Diabetes Association*	100g	95	180	155	140
American College of Obstetrics and Gynecology*	100g	105	190	165	145

*(Agarwal, 2010; Jiménez-Moleón et al., 2002; Mpondo, Ernest, & Dee, 2015)

CHAPTER TWO: AIMS

Objective: The study is an analysis of data electronically retrieved from electronic medical/health records to quantify the risk imposed by GDM for preeclampsia in primigravid women.

Aim: Determine to what extent GDM increases the risk for preeclampsia

Null hypothesis: There is no impact of GDM diagnosis on risk for developing preeclampsia.

Alternate hypothesis: The increased risk for pre-eclampsia in women with a positive diagnosis of GDM.

Purpose: The purpose of this study is to examine the association of GDM for preeclampsia in primigravid women and determine the racial/ethnic differences. This would ultimately create a platform through which adverse outcomes of pregnancy might improve in the United States. We expect to demonstrate GDM as a substantial risk factor for preeclampsia.

CHAPTER THREE: METHODOLOGY

Dataset

The study was conducted using data electronically retrieved from the electronic medical records of a large integrated health system in Florida. The multispecialty physician group and hospital affiliate serve approximately 6,000 pregnant women per year. The communities served have a demographic composition of approximately 71% White/Caucasian and 17% Black/African American, and 12% other. Ethnicity is approximately 41% Hispanic and 59% non-Hispanic. Data were extracted from electronic health records with the assistance of Information Systems staff and contractors and generated a dataset encompassing approximately 10 years' worth beginning in 2007.

Study Population and Design

The data for this analysis included pregnancy records for patients at least 18 years of age over a six-year period beginning in 2011 – 2016. The analysis was limited to primigravida women with a singleton pregnancy. The risk of preeclampsia for gestational diabetes mellitus (GDM) positive women was compared to non-GDM positive women. GDM and preeclampsia were identified by using *International Classification of Diseases*, Tenth Revision (ICD-10) records. This is a descriptive study conducted using data electronically retrieved from electronic medical records of patients. In this study preeclampsia was the outcome of interest (i.e. dependent variable) and GDM was exposure (i.e. independent variable).

Data Management

The data were extracted into multiple excel spreadsheets with files containing information related to the mother's medical history, demographics, number of visits to the hospital during pregnancy, and the medical history of the child. After data extraction, identifiers were reduced/limited by the investigators. Then as per the requirement of this thesis, data were cleaned, and files matched by the patient's obfuscated hospital identification number. Figure 1 presents the steps used for obtaining the desired study population.

1) The file with the mother's demographic information was used to obtain a desired population sample size of n = 8167 after restricting 'Number of Babies' to one and 'Number of Pregnancies' to one. The observations with "Null" entries for the variable 'Number of Pregnancies'; information for the mother's subsequent pregnancy was used to infer the parity of the previous delivery in records with missing data for this variable.
2) In the entire dataset, there were 871 observations considered to be 'screen fail' (the patients who did not meet the inclusion criteria for the overall study) out of which 797 were present in mother's demographics with restriction criteria. These observations were removed from the dataset.
3) The mother's medical history file includes information of diagnosis as per ICD-9-CM and ICD-10-CM codes for each pregnancy visit. In this study, we only used the ICD-10-CM code to obtain information for diagnosis as ICD-9-CM were converted to ICD-10-CM.
4) The desired inclusion and exclusion variables were identified as per ICD-10-CM codes which were present in mother's medical history file. The women with the diagnosis of GDM and preeclampsia were included. Women with the diagnosis of type 1 and type 2

diabetes mellites, hypertension other than gestational, and eclampsia were excluded from the analysis. Table 2 and Table 3 present the ICD 10 CM codes for inclusion variables and exclusion variables used in this thesis.

5) As per the restriction criteria only 3017 observations from the entire mother's medical history file (irrespective of the diagnosis) matched with the demographics file. It was assumed that women without a linked medical history had no diagnosed medical condition prior to the index pregnancy (n = 4631).
6) Moreover, from the mother's medical history file, only those observations were included which align with the date of 1st pregnancy listed in the mother's demographic file. As file with mother's medical history and demographics had different dates, therefore, to acquire the diagnosis date to correspond with first pregnancy, new variables "daysdigtovisit" was created where we subtracted start date (information when women visited the hospital obtained from demographics file) from noted date (when diagnosis was made obtained from medical history file) and only considered women if the difference was within 9 calendar months. The dataset contains n=2130 observations, after accounting that date of diagnosis matches the current pregnancy and there are no duplicate observations and 887 observations did not get matched.
7) The file named 'Mother visit' includes information on the weight and height of women for each pregnancy visit. We used the information about weight and height to calculate the BMI (703 * weight (lbs) / [height (in)] ^{2}) of women. After merging the file with main demographics files less than 50 percent of women had information for BMI. The dataset does not allow to gather information regarding pre-pregnancy BMI or when was BMI measured during pregnancy. In order to pertain, variable 'recentbmi' was created where

the date of last menstrual period was subtracted from the start date (when women visited the hospital for the first time), this provides the information about in which trimester BMI was calculated. If BMI was calculated in first trimester, we considered it as pre-pregnancy BMI. Therefore, variable BMI was excluded from the final model and a sub-analysis was conducted to find the association of BMI with GDM and preeclampsia.

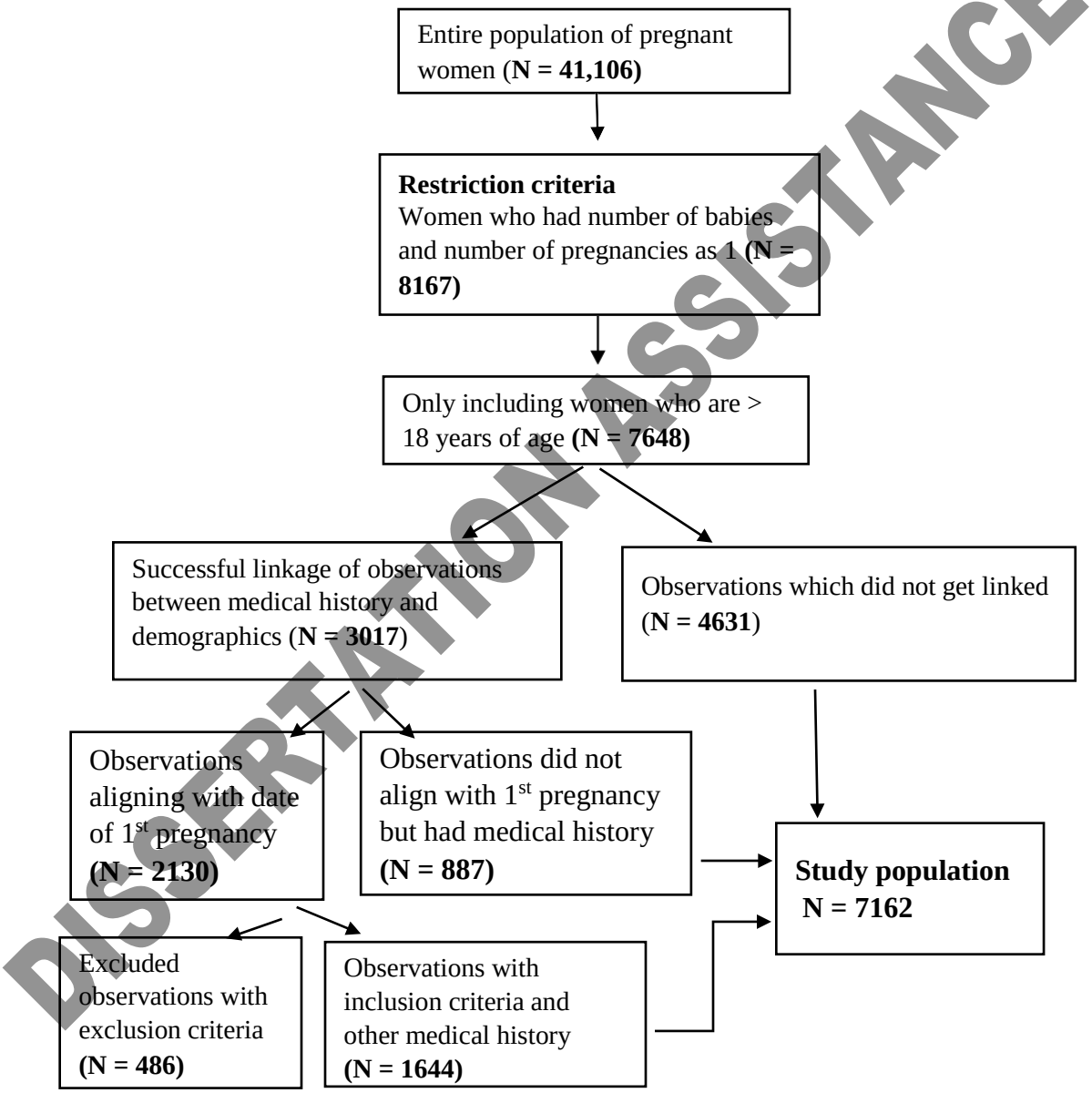

Figure 1: Final Study Population

Measures

In this study, covariates were included if a positive association with the dependent variable was detected in the existing literature and available in the acquired dataset. Table 4 lists details concerning the variables used in this study.

Dependent variable. Preeclampsia: a binominal variable was used as an outcome measure where "1 = preeclampsia positive" and "0 = preeclampsia negative". The population sample size of 7,162 a total of 532 primigravid women were diagnosed with preeclampsia.

Independent variable. GDM: a binominal variable where "1 = GDM positive" and "0 = GDM negative". A total of 286 women were diagnosed with GDM in this study population.

Covariates. The covariates analyzed were identified from evidence-based literature (Feig, Zinman, Wang, & Hux, 2008; MacNeill, Dodds, Hamilton, Armson, & VandenHof, 2001; Schneider et al., 2012; Wen et al., 2012; Wendland et al., 2008; C. Zhang et al., 2016) includes mother's age, race, smoking status, and body mass index. They were used to adjust for confounding and examine their interaction with dependent and independent variables. As the dataset does not have a specific classification for the maternal race and there was only one option for race/ethnicity for each patient. Therefore, for this study maternal race was categorized as per CDC classification and we grouped race into five categories: White, African American, Asian, Latino, and Others. The detailed categorization of race is present in Table 5. Mother's smoking status has four categories: former smoker, never smoker, current smoker/exposure to smoke includes current every day or someday smoker, light or heavy tobacco smoker, smoker-current status unknown, passive smoke exposure -never smoker and others/unknown category contains those patients who were never assessed and unknown if ever smoked. Moreover, BMI was

classified into quartiles i.e. underweight (BMI < 18.5), normal weight (i.e. BMI in 18.5 - < 25), overweight (i.e. BMI in 25 - < 30) and obese (i.e. BMI ≥30) as per the CDC guidelines.

Statistical Analysis

Descriptive statistics were conducted initially to understand the frequency and range of each variable used in the study. The use of a pearson chi-square test to analyze the results for categorical variables whereas t-test to interpret the results for continuous variables and address the appropriate level of significance and p-value in order to understand whether there is an association between the dependent, independent variable and other covariant used. Furthermore, using the logistic regression model we conducted the bivariable and multivariable analysis to estimate the effect of GDM and other covariant over preeclampsia. Pearson chi-square was used to assess the significance of each variable. Potential confounders including age, race and smoking status of the mother were identified on theoretical grounds and were controlled by including them in the multivariable analysis model simultaneously. Another model was created to test for two-way interactions between exposure of interest (GDM) and age, race and smoking status of the mother. Later the comparison between the main model and a model with two-way interactions was conducted and we identified that interaction terms were not important for the model as per the results of the likelihood test. As less than 50% of the population had information with BMI, therefore another model of logistic regression was used to conduct a sub-analysis in order to understand the confounding effects of BMI over GDM and preeclampsia. The analysis was done by using SAS 9.4 version.

Table 2: ICD-10-CM codes used to identify GDM and preeclampsia

Gestational Diabetes Mellitus		Preeclampsia	
Diagnosis name	**ICD-10-CM code**	**Diagnosis name**	**ICD-10-CM code**
GDM class B, C, H	IMO001	Hypertension in pregnancy-preeclampsia	IMO002/O14.15
GDM class A1/A2	O24.410/ O24.419	Mild preeclampsia in unspecified/ 2nd /3rd trimester/ delivered/postpartum	O14.00/O14.02/O14.03/ O14.04/O14.05
GDM controlled by Insulin/ Oral hypoglycemic drugs/ Diet	O24.414/ O24.415/ O24.420	Severe preeclampsia in unspecified/ 2nd /3rd trimester/ delivered/postpartum	O14.10/O14.12/ O14.13
GDM in childbirth/ postpartum	O24.429/ O24.439	Preeclampsia in unspecified/ 2nd /3rd trimester/ delivered/postpartum	O14.90/O14.92/ O14.93/O14.94/O14.95
GDM in puerperium diet/ Insulin controlled	O24.430/ O24.434	Pregnancy induced or Gestational hypertension in unspecified/ 2nd /3rd trimester/ delivered/postpartum	O13.1/O13.2/O13.3/ O13.4/O13.5/O13.9

Table 3: ICD 10 records excluded from the analysis.

Condition	Eclampsia in pregnancy/2nd trimester/ delivered/ postpartum	Type 1 diabetes mellitus predisposing with any condition	Type 2 diabetes mellitus predisposing with any condition	Hypertension other than gestational
ICD 10 records	O15.00/02/1/9	E08.00/01/9/10/22 E10.8/9/10/21/22/ 29/319/40/42/649/ 65/ O24.911/912/913/ 919	E11.00/01/8/9//21/29/ 42/49/65/69 O24.111/112/113/119 /311/312/313/319	I10/I12.0 I15.1/2/8/9 I16.0/1/9 O10.012/013/019/ 911/912/913/919 O11.9 O16.1/2/3/4/5/9

Table 4: Information of the variables used in the study

Variables	Variable name	Variable description	Value (s) of variable	Type of variable
Preeclampsia	*Preeclampsia*	Primigravida women and with a history of singleton pregnancy who were diagnosed as mild, severe or gestational hypertension during pregnancy as per ICD 10 records.	1 – Preeclampsia positive 0 – Preeclampsia negative	Dependent
Gestational diabetes mellitus	*GDM*	Primigravida women and with a history of singleton pregnancy who were diagnosed with GDM during the pregnancy by ICD 10 records.	1 – GDM positive 0 – GDM negative	Independent
Age of mother	*Age_mother*	Birth date was used to calculate age of mother	18 – 24 years old 25 – 29 years old 30 – 34 years old 35 – 39 years old 40 – 44 years old 45 – 55 years old	Control
Race of mother	*Race*	Race and ethnicity of mother	1 – African American 2 – Asian 3 – Latino 4 – White 5 - Others/Unknown	Control
Smoker	*Smoking status*	Smoking status of mother	1 – Former smoker 2 – Current smoker/ Exposure of smoke 3 – Never smoker 4 – Unknown	Control
Body mass index	*BMI*	Underweight: <18.5 Normal weight: 18.5 - <25 Overweight: 25 – < 30 Obese: > 30	1 – Underweight 2 – Normal weight 3 – Overweight 4 - Obese	Control

Table 5: Classification of Maternal Race

Race categorization used in this study	Categories present in data set
White	White
African American	Black or African American, African (Continental), West Indian, Haitian
Asians	Arab or Middle Eastern, Asian Indian/Indian Sub-Continent, Asian, Chinese, Japanese, Vietnamese, Korean, Filipino
Latino	Cuban, Puerto Rican (Island and Mainland), Mexican
Others	Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Guamanian or Chamorro, North African (non-black), European Descent, Unknown, Null, Other, Patients Refused to Answer

CHAPTER FOUR: RESULTS

During the six-year period 2011 – 2016, there were a total of 41,106 pregnancy records in the dataset. Among these, 7,162 pregnancy records were selected after restricting the data and removal of observations present under exclusion criteria.

GDM and Preeclampsia

GDM occurred in 286 (3.9%) and preeclampsia in 532 (7.4%) of all primigravida women with singleton birth (n = 7,612). Only 26 (0.4%) women were identified as having both diseases (Fig 2). Out of the total population of women diagnosed with GDM (n = 286) approximately 9.1% had preeclampsia whereas 7.4% of women without GDM (n = 6,876) were diagnosed with preeclampsia.

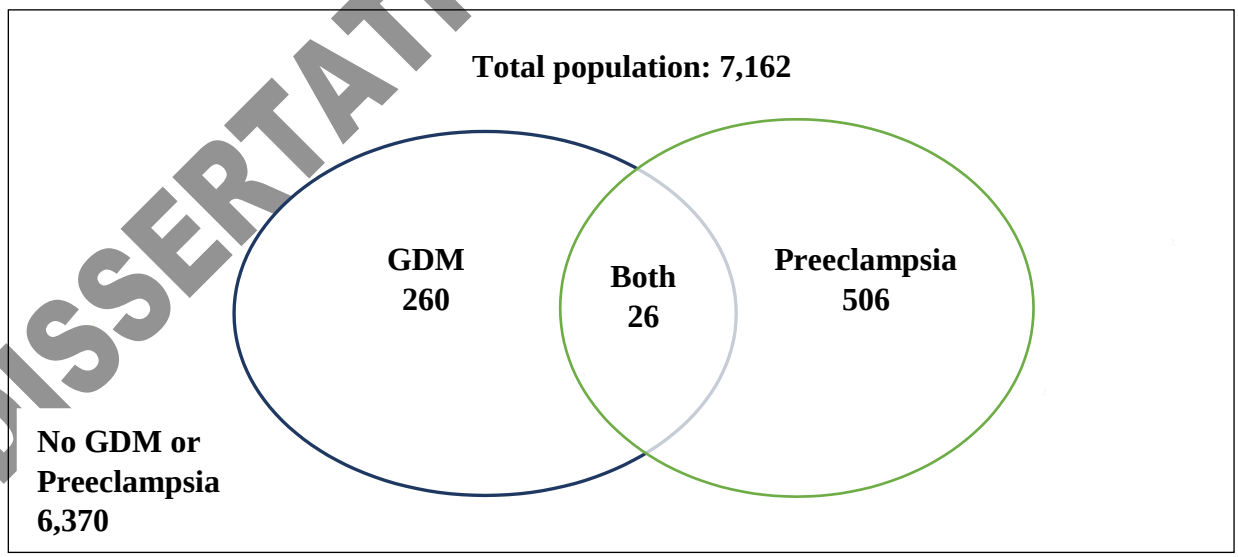

Figure 2: Prevalence of preeclampsia and GDM

Correlation between Covariates and both Dependent and Independent Variable

In order to present the demographics and associated risk factors, frequencies for each variable were provided and stratified by variables GDM and preeclampsia (Table 6). Mother's age and race were found to be statistically significantly different among mother's with and without GDM as per as mother with and without preeclampsia

Mother's age was significantly associated with both GDM ($p<0.0001$) and preeclampsia ($p = 0.0026$). Moreover, the rates of GDM increased with increasing maternal age; preeclampsia did not have similar patterns. Around 10.5% of women between 18 – 24 years of age were positive for preeclampsia and only 1.7% had GDM whereas, 8.9% of women among 25-29 years of age were had preeclampsia and 2.8% had GDM. Moreover, 5.6% of women among 45-55 years of age had preeclampsia and 7.7% had GDM. Table 6 has the results of this analysis with other categories of age. The mother's race also had a statistically significant association with both GDM ($p<0.0001$) and preeclampsia ($p = 0.0063$). Around 8.8% of African Americans were diagnosed with preeclampsia and 3.1% had GDM, 4.3% of Asians had preeclampsia and 8.5% had GDM while the percentage of Latinos who suffered from these conditions were higher in both preeclampsia and GDM (9.5% and 10.2% respectively). Among Whites 7.6% were diagnosed with preeclampsia and only 3.7% had GDM. The smoking status of the mother was not statistically significant for either of the conditions. Among women who were current smoker or had exposure to smoke, 6.9% were diagnosed positive for preeclampsia and 4.4% had GDM. However, around 7.1% of women who never smoked developed preeclampsia and 3.8% developed GDM. The results are presented in Table 6.

Bivariate and Multivariable Analysis

The results of bivariable (crude odds) and multivariable (adjusted odds) logistic regression analyses are presented in Table 7. Effect modification between mother's age and race and the association between GDM and preeclampsia were examined. There was no evidence of effect modification for both maternal characteristic (mother's age and race p value 0.9828 and 0.2123 respectively). Thus, the final model was conducted without using interaction terms. In both crude and adjusted models, the odds ratio (OR) was not statistically significant for the association between GDM and preeclampsia. However, in comparison to women without GDM, the risk of preeclampsia was higher among women with GDM (OR=1.33; 95% CI 0.9,2.1; p value 0.1826). The age of the mother was significantly associated (p value 0.0132) with the development of preeclampsia. The results of crude and adjusted OR showed that women among 30 – 34 years of age were less likely to develop preeclampsia (OR = 0.61; 95% 0.4,0.9; p value 0.0140) compared to women in 18 – 24 years of age group. Although results were not statistically significant, women 35 – 39 years and 40 – 44 years of age were at lower risk for preeclampsia (p value 0.0480 and p value 0.0706 respectively) compared to women in 18 – 24 years. Similarly finding of both crude and adjusted OR show Asian women were less likely to develop preeclampsia (OR=0.56; 95% CI 0.3, 0.9; p value 0.0166) compared to White women. The women in the Other Race category were also at lower risk for preeclampsia compared to White. Although the results show that African American (OR=1.08; 95% CI 0.8, 1.3; p value 0.5150) and Latino women (OR=1.13; 95% CI 0.7, 1.7; p value 0.5957) have a slightly elevated risk of preeclampsia compared to White women, though the results were not significant. In this population smoking status of women has no statistical significance over the development of preeclampsia.

Sub-analysis. The sub-analysis (n= 3,586) was conducted to examine the association of mother's BMI with preeclampsia and GDM. Among women whose BMI was calculated in the first trimester (n = 1,150) assuming it to correspond to pre-pregnancy BMI; 53 women were diagnosed with GDM and 74 women had preeclampsia. Out of the total women diagnosed with GDM who's BMI was calculated in first trimester, approximately 56.6% (n=30) were obese, 30.1% (n = 16) were overweight and 13% (n =7) were in normal weight category. Whereas the proportion of women diagnosed with preeclampsia, approximately 64.8 % (n = 48) were obese, 25.7% (n = 19) overweight and 8% (n = 6) were in normal weight category when BMI was calculated in the first trimester. Moreover, higher percentage of women diagnosed with these conditions were either overweight or obese, if BMI was calculated in the second or third trimester of pregnancy. Table 8 represents the results of these analyses.

After introducing BMI (irrespective during which trimester BMI was calculated) and other potential confounders into a sub-analysis logistic regression model, we found that BMI (p value <0.0001) has a statistically significant association while age (p value 0.4491) and race (p value 0.1689) of the mother were no longer associated with GDM and preeclampsia. GDM women in obese category were 2 times more likely to develop preeclampsia (OR=2.18; 95% CI 1.5, 3.2; p value <.0001). The results of crude and adjusted odds of the sub-analysis presented in Table 9.

Table 6: Population statistics, by variable of interest, among women with and without GDM and preeclampsia

Variable	Total (N)	With GDM		Without GDM			With preeclampsia		Without preeclampsia		
		N	%	N	%	p-value*	N	%	N	%	p- value
Age of mother*						<.0001					0.0021
18 – 24 years	351	6	1.7	345	98.3		36	10.5	315	89.7	
25 – 29 years	2370	66	2.8	2304	97.2		211	8.9	2159	91.1	
30 – 34 years	2183	85	3.9	2098	96.1		136	6.2	2047	93.8	
35 – 39 years	1570	86	5.5	1484	94.5		107	6.8	1463	93.2	
40 – 44 years	545	32	5.9	513	94.1		34	6.2	511	93.8	
45 – 55 years	143	11	7.7	132	92.3		8	5.6	135	94.4	
Race of mother*						<.0001					0.0024
African American	1501	47	3.1	1454	96.9		132	8.8	1369	91.2	
Asian	460	39	8.5	421	91.5		20	4.3	440	95.6	
White	3565	131	3.7	3434	96.3		273	7.6	3292	90.5	
Latino	264	27	10.2	237	89.8		25	9.5	239	92.3	
Other/Unknown	1372	42	3.1	1330	96.9		82	5.9	1290	94.0	
Smoking status						0.1875					0.1715
Former smoker	1013	37	3.7	976	96.4		71	7.0	942	92.9	
Current smoker/ Exposure of smoke	362	17	4.7	345	95.3		27	7.5	335	92.5	
Never smoker	5571	229	4.1	5342	95.9		426	7.7	5145	92.4	
Unknown	216	3	1.4	213	98.6		8	3.7	208	96.3	

*p value <0.05 Pearson chi- square

Table 7: Crude and Adjusted Odds Ratios for Preeclampsia

Women Diagnosed with Preeclampsia		
Variables	**Crude Odds OR (95% CI)**	**Adjusted Odds OR (95% CI)**
Gestational diabetes mellitus		
Without GDM	1.00	1.00
With GDM	1.26 (0.83 – 1.90)	1.33 (0.87 – 2.08)
Age of mother		
18 – 24 years	1.00	1.00
25 – 29 years	0.85 (0.59 – 1.24)	0.87 (0.60 – 1.28)
30 – 34 years	0.58 (0.39 – 0.86) **	0.61 (0.41 – 0.90) **
35 – 39 years	0.64 (0.43 – 0.95) **	0.67 (0.41 – 1.01)
40 – 44 years	0.58 (0.36 – 0.95) **	0.62 (0.37 – 1.01)
45 – 55 years	0.52 (0.24 – 1.14)	0.57 (0.25 – 1.27)
Race		
White	1.00	1.00
African American	1.16 (0.94 – 1.44)	1.08 (0.86 – 1.33)
Asian	0.55 (0.34 – 0.87) **	0.56 (0.35 – 0.91) **
Latino	1.26 (0.82 – 1.93)	1.13 (0.73 – 1.74)
Others/Unknown	0.77 (0.59 – 0.98) **	0.74 (0.56 – 0.95) **
Mother Smoking Status		
Never Smoker	1.00	1.00
Former Smoker	0.91 (0.70 – 1.18)	0.88 (0.68 – 1.15)
Current Smoker/Exposure of smoke	0.97 (0.65 – 1.46)	0.91 (0.60 – 1.37)
Unknown	0.46 (0.22 – 0.95)	0.48 (0.23 – 0.98)

****** Statistically significant

Table 8: Cross tabulation of BMI with GDM and Preeclampsia

BMI calculated in which trimester	Mother's BMI	With GDM N (%)	Without GDM N (%)	Chi-square <.0001	With Preeclampsia N (%)	Without Preeclampsia N (%)	Chi-square <.0001
First	Underweight	0	25 (2.3)		1 (1.3)	24 (2.3)	
	Normal weight	7 (13.2)	277 (25.5)		6 (8.1)	278 (25.8)	
	Overweight	16 (32.2)	355 (32.3)	0.0546	19 (25.7)	352 (32.7)	<.0001
	Obese	30 (56.6)	440 (40.1)		48 (64.8)	422 (39.2)	
Total	1150 (100)	53 (4.6)	1097 (95.4)		74 (6.4)	1076 (93.5)	
Second	Underweight	0	16 (1.5)		1 (1.1)	15 (1.5)	
	Normal weight	6 (11.5)	271 (25.3)		19 (21.1)	258 (25.0)	
	Overweight	16 (30.7)	341 (31.9)	0.0500	20 (22.2)	337 (32.6)	0.0527
	Obese	30 (57.7)	441 (41.3)		50 (55.6)	421 (40.8)	
Total	1121 (100)	52 (4.6)	1069 (95.4)		90 (8.0)	1031 (91.7)	
Third	Underweight	0	5 (0.5)		0	5 (0.5)	
	Normal weight	9 (9.7)	191 (21.0)		12 (17.9)	188 (20.1)	
	Overweight	28 (30.1)	350 (38.5)	0.0012	16 (23.8)	362 (38.8)	0.0316
	Obese	56 (60.2)	362 (39.8)		39 (58.2)	379 (40.6)	
Total	1001 (100)	93 (9.3)	908 (90.7)		67 (6.7)	934 (93.3)	

Table 9: Crude and Adjusted Odds Ratio for Preeclampsia with BMI as confounder

	Women Diagnosed with Preeclampsia	
Variables	**Crude Odds OR (95% CI)**	**Adjusted Odds OR (95% CI)**
Gestational diabetes mellitus		
Without GDM	1.00	1.00
With GDM	1.00 (0.57 – 1.75)	0.86 (0.48 – 1.53)
BMI		
Normal weight	1.00	1.00
Underweight	0.89 (0.20 – 3.84)	0.88 (0.21 – 3.82)
Overweight	1.03 (0.67 – 1.58)	1.04 (0.67 – 1.59)
Obese	2.20 (1.51 – 3.20) **	2.18 (1.49 – 3.19) **

CHAPTER FIVE: DISCUSSION

Study Summary

In this thesis, our aim was to examine the association between GDM and preeclampsia in primigravid women. The analysis was conducted based on the pregnancy records for patients obtained using data electronically retrieved from medical records of a large integrated health system in Florida. Moreover, potential confounders and effect modifiers were determined from existing literature and availability in the dataset. We used the bivariable and multivariable logistic regression model in order to identify the presence of any associations, confounders, and modifiers. This study found that the prevalence of preeclampsia among GDM women is slightly higher compared to women without GDM. However, the results were not significant (p value 0.1417) but the trend suggests a meaningful difference.

Exposure and Outcome of Interest

Studies have indicated that GDM women are at higher risk for preeclampsia and its related complications (Östlund et al., 2004; Schneider et al., 2012; Wen et al., 2012; Yogev et al., 2004). The results of this thesis indicate the overall prevalence of GDM, and preeclampsia was 3.99% and 6.93% respectively. These rates were comparatively low to rates of GDM (4.7%) and preeclampsia (3.7 per 100 deliveries) in the state of Florida (Bardenheier et al., 2013, 2015; S. Y. Kim et al., 2012; Mulla, Gonzalez-Sanchez, & Nuwayhid, 2007). Out of the total number of women diagnosed with GDM in this study, around 9.09% suffered from preeclampsia compared to 6.84% of women without GDM. However, in this study, the results portray no significant

association between GDM and preeclampsia and only 0.4% of all pregnant women developed both conditions in first pregnancy. These results were consistent with some studies (Goldman, Kitzmiller, Abrams, Cowan, & Laros, 1991; Schaffir, Lockwood, Lapinski, Yoon, & Alvarez, 1995). Goldman et al. (1991) also noted the rates of preeclampsia doubled in GDM women but did not find any statistical significance. However, the findings of this thesis were inconsistent with previously published case-control and cohort studies examining this association (Farahvar et al., 2019; Lee et al., 2017; Östlund et al., 2004; Weissgerber & Mudd, 2015; Wen et al., 2012; Wendland et al., 2008). Schneider et al. (2012) compared the rates of preeclampsia at a different severity level of GDM determined by the Fasting Plasma Glucose (FPG) levels from the OGTT test. The authors noted the risk of preeclampsia in GDM women increased at each level of severity and who developed preeclampsia had higher OGTT level. Moreover, researchers noted that GDM significantly increases the risk of preeclampsia especially in younger and older age, nullipara and obese women (Bryson, Ioannou, Rulyak, & Critchlow, 2003; Östlund et al., 2004; Wendland et al., 2008; Yogev et al., 2004). Furthermore, we found the risk of preeclampsia in GDM women was higher among 18 – 24 and 25 – 29 years old. In our study Asian women were less likely to suffer from preeclampsia compared to White women. The results were not significant for other races. In this study, smoking status of mother does not seem to be correlated with either of the diagnoses. Nevertheless, the overall findings have been inconsistent with other reports (Bryson et al., 2003; Östlund et al., 2004; Weissgerber & Mudd, 2015; Wendland et al., 2008; Yogev et al., 2004). This may be attributed to the singleton births and parity status of women and exclusion criteria (eclampsia, type 1 and type 2 DM and hypertension) applied to the study.

Other Findings

The results from this thesis confirmed that the rates of GDM significantly and progressively increased with maternal age. These results align with the findings of other previously conducted studies considering maternal age to be a predictive factor for the development of GDM (Bardenheier et al., 2013; Farahvar et al., 2019; Lao, Ho, Chan, & Leung, 2006). This also supports the recommendation of the American Diabetes Association; considering 25 years of age as a cut off for screening for GDM (Lao et al., 2006). While the percentage of preeclampsia was higher among women between 25 – 29 (8.4%) and 30 – 45 years of age.(6.4%) among researchers examining the trends in preeclampsia by maternal age mentioned increase in rates of preeclampsia in young (15 -19 years old) and older (≥30 years old) age women (Ananth et al., 2013; Cavazos-Rehg et al., 2015; Sheen et al., 2019). In this study, the percentage of GDM were higher among Asians and Latino women compared to African American and White population. Our findings for racial/ethnic differences in GDM are consistent with several previous studies (Bardenheier et al., 2013, 2015). The racial differences in rates of preeclampsia somewhat differ from the existing literature as preeclampsia rates are lower among Hispanic women whereas in this study around 8.6% of the total Latino women were diagnosed with preeclampsia (Caughey, Stotland, Washington, & Escobar, 2005; Cavazos-Rehg et al., 2015; Samadi et al., 1996). This could be because the composition of Latino group in this study is different and they can have different risks. Out of the total population of African Americans and Whites around 7.9% and 7.3% respectively suffered from preeclampsia. The findings of mother's race are in agreement with previous studies (Caughey et al., 2005; Ghosh et al., 2014).

Existing literature suggests several reasons for racial and ethnic differences in the rates of these conditions which include maternal age, pre-pregnancy BMI and history of fetal death or cesarean section (Bardenheier et al., 2013; Nguyen et al., 2012; Xiong, Saunders, Wang, & Demianczuk, 2001). Moreover, this study shows that mother's age and race have an independent association with GDM and preeclampsia. For this study population, the mother's smoking status was not associated with either of the conditions. Studies have shown a negative correlation between smoking with preeclampsia but it still remains a controversy (Östlund et al., 2004; Schneider et al., 2012).

Evidence-based literature suggest BMI is one of the most important predictors and modifiable risk factors for both GDM and preeclampsia (Bardenheier et al., 2013; Bryson et al., 2003; Farahvar et al., 2019; Jeyabalan, 2013; Östlund et al., 2004; X. Zhang & Xiao, 2019). Weissgerber and Mudd (2015) and X. Zhang and Xiao (2019) noted excessive gestational weight gain in GDM women also increases the risk of preeclampsia. Weissgerber and Mudd (2015) identify first-trimester obesity (BMI ≥ 27kg/m2) as one of the prime factors leading to preeclampsia in GDM women. The presence of inconsistency in the literature related to the association between pre-pregnancy obesity and the risk of preeclampsia and GDM. Some studies associated increasing rates of preeclampsia in GDM women to pre-pregnancy obesity (Schneider et al., 2012; Weissgerber & Mudd, 2015) whereas X. Zhang and Xiao (2019) found no association. Even with the limited availability of data over BMI, in this study BMI was significantly associated with both GDM and preeclampsia.

Limitations of the Study

The sample size of the study limits the generalizability of the results. Moreover, this dataset only has limited information on maternal demographic characteristics, thus limiting the

estimation of other associated risk factors and controlling them to confounding which are addressed in existing literature (MacNeill et al., 2001; Schneider et al., 2012; Wen et al., 2012; C. Zhang et al., 2016). As the data was obtained using medical records of patients another shortcoming could be reporting and documentation bias which increases the probability of misclassification of variables such as smoking status of the mother. The high frequency of missing data could be assumed because of non-standardized methods used in data collection. Moreover, the inability to link approximately 60% of records from mothers' demographics file to the mother's medical history file was another possible limitation of the study. Furthermore, more than 50% of population did not have information for BMI. There was no information on pre-pregnancy weight which limits the estimation of weight gain during pregnancy. As higher amount of weight gain which is above recommended criteria increases the risk of perinatal complications (Bouvier et al., 2019; Hedderson, Gunderson, & Ferrara, 2010). Another limitation was inconsistency in the availability of race/ethnicity data as Hispanic ethnicity was not documented. In addition to this, another limitation of the study was the inability to determine the methods used for screening and diagnosing of both conditions as this information is not available in the dataset.

CHAPTER SIX: PUBLIC HEALTH IMPLICATIONS

Literature suggests that GDM and preeclampsia exposes the mothers and newborns to adverse health outcomes (Larrabure-Torrealva et al., 2018; Lee et al., 2017; Ma et al., 2013; Veeraswamy et al., 2012; Wen et al., 2012). Few studies state GDM as one of the risk factors for preeclampsia (Farahvar et al., 2019; Östlund et al., 2004; Weissgerber & Mudd, 2015). This study found that the prevalence of preeclampsia among GDM women is slightly higher compared to women without GDM. However, the results were not significant (p value 0.1417). Nevertheless, the trend in conjunction with the existing body of literature suggest it is necessary to develop programs and interventions to reduce the rates of GDM and preeclampsia at the patient and provider level.

The patient-level campaigns should be developed to impart knowledge and create awareness among the population about the associated risk factors and health consequences of GDM (Evert & Hei, 2006; Price, Lock, Archer, & Ahmed, 2017). The programs can be used to provide information about available resources and encouraging women, especially high-risk those at high risk for developing GDM and preeclampsia, to undergo periodic antenatal care and checkups to get evaluated for GDM early in the pregnancy. Moreover, all pregnant women should be encouraged for regular or leisure-time physical activities during and/or before pregnancy and motivated to adopt healthy eating habits. In the study examining the effects of physical activity during pregnancy, stated that women who perform physical activity during

pregnancy not have better pregnancy outcome, but also improved physical and emotional well-being and less stress and anxiety during pregnancy (Hegaard, Pedersen, Bruun Nielsen, & Damm, 2007). Moreover, intake of the high amount of ultra-processed food and a diet with high sucrose and fatty acids are associated with increased risk for developing both conditions (Clausen et al., 2001; Park et al., 2013). Due to very little adherence to the guidelines for GDM patients, the health care system is failing to bring GDM women back for screening during antenatal and postnatal period. Thus, annual training for health care providers should be conducted to emphasize screening high-risk women early in pregnancy which would improve identification, provide better care and alleviate the associated long-term effects and complications (Morampudi, Balasubramanian, Gowda, Zomorodi, & Patil, 2017). Moreover, as it occurs due to the stereotypes or assumptions which exist in the society impacting the judgment of providers might result in delivery of insufficient information and disparities in providing care and treatment (FitzGerald & Hurst, 2017; Maina, Belton, Ginzberg, Singh & Johnson, 2018). It can also lead to false assumptions and negative outcomes mainly impacting group of disparity (Maina et al., 2018). This could be reduced by evaluating the knowledge, attitude, and practices followed by health care professionals which could provide an insight into the gaps in the system (FitzGerald, Martin, Berner, & Hurst, 2019).

Improving the current health status of society requires the cumulative efforts of the government and public health practitioners. Providing adequate care and information to a diverse community establishes better patient-provider relationships that lead to better emotions and mental support to these women. Developing optimal strategies and interventions which are affordable, easily accessible to everyone irrespective of age/gender/race and ethnicity would ultimately raise the quality of general well-being of community.

CHAPTER SEVEN: FUTURE RECOMMENDATION

Future research is necessary to explore the impact of gestational age at the time of diagnosis with these conditions which was not evaluated in this study. As in this study, BMI was significantly associated with GDM and preeclampsia. However, we were not able to explore the relationship of gestational weight gain. Therefore, there is the need for future research evaluating the effect of gestational and interpregnancy weight gain over GDM and preeclampsia. Moreover, conducting a trend analysis to understand the change in rates of these conditions over the time period would help while implementing preventive interventions. Case-cohort study should be performed with this population to further explore the associated environmental and genetic risk factors with preeclampsia in GDM women. Moreover, integrating GIS methods would be beneficial if the collected data is also linked with geolocations. This would help identification of areas with higher prevalence for these conditions and help while implementing preventive interventions.

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