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The Association between Advanced Maternal Age and Adverse Hypertensive and Diabetic Complications During Pregnancy:

A Six-year Retrospective Cohort Study in Metro Atlanta, USA

By

Momoko Kitami
Master of Public Health

Global Epidemiology

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By

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M.D., Gunma University School of Medicine, 2009
B.S., Duke University, 2004

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

The Association between Advanced Maternal Age and
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A Six-year Retrospective Cohort Study in Metro Atlanta, USA

By

Momoko Kitami

OBJECTIVE: To investigate the effects of advanced maternal age on adverse hypertensive and diabetic complications of pregnancy, in relation to other major risk factors.
METHODS: A retrospective cohort study using Kaiser Permanente Georgia electronic health data of pregnant women receiving prenatal care in 12 Kaiser-affiliated Obstetrics and Gynaecology facilities between January 1, 2005 and August 31, 2011, with linked Georgia Birth Certificate data. Women were divided into two age groups: 1) reference group who were 35-39 years old, and 2) advanced maternal age (AMA) group who were 40 years and older. Adjusted risk ratios (aRR) were calculated after adjusting for correlation among women with multiple pregnancies, and relevant confounders (maternal race, obesity, infertility, gravidity, maternal education, marital status, and pre-existing medical conditions) using log-Binomial or log-Poisson regression analysis.
RESULTS: A total of 1181 pregnancies of 1096 women (939 women in reference group, 157 in AMA group) were included in the study. Risk of chronic hypertension was significantly higher in the AMA group (adjusted risk ratio [aRR], 2.05; 95%CI, 1.48-2.86), but risk of transient hypertension (aRR, 1.07; 95%CI, 0.51-2.22), mild preeclampsia (aRR 1.31; 95%CI, 0.61-2.81), severe preeclampsia/eclampsia (aRR 0.87; 95%CI, 0.26-2.86), chronic diabetes (aRR 0.74; 95%CI, 0.37-1.50), and gestational diabetes (aRR 0.97; 95%CI, 0.59-1.59) were not significantly increased in the AMA group. When risk of having any hypertensive complications was evaluated separately for white and black maternal race, AMA remained a significant risk factor among blacks (p=0.002), but note whites (p=0.15). Although risk of having preeclampsia or eclampsia was more fully explained by history of chronic hypertension and marital status than AMA, no significant risk factor was identified for transient hypertension. Obesity, primigravida, and Asian maternal race were identified as more significant risk factors for gestational diabetes compared to AMA.
CONCLUSION: Advanced maternal age is an important risk factor for chronic hypertension, but other risk factors such as obesity, maternal race, gravidity, and pre-existing medical conditions may play a larger role in the development of preeclampsia, eclampsia, and gestational diabetes. Strength of association of these risk factors may vary depending on maternal race.

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Finally, I would like to dedicate this thesis to my beloved father, Yoshiro Kitami, who courageously battled cancer during my time at Emory, and passed away on April 22, 2013. I am forever grateful for his quiet love and humor.

Table of Contents

List of Tables in Chapter 1. Literature Review

List of Tables in Chapter 2. Thesis Manuscript

multigravid women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data (n=834)

Table 4A. Crude association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy complications of both primigravid and multigravid women, who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data, including multiple gestations by the same women during the study period (n=1181)

Table 4B. Adjusted association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy complications of both primigravid and multigravid women, who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data, including multiple gestations by the same women during the study period (n=1181)

Table 5. Crude association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy outcomes for pregnancies of women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011 (n=2167)

Table 6. Crude association of any hypertensive complications during pregnancy and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Table 7. Crude association of transient hypertension and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Table 8. Crude association of preeclampsia/eclampsia and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Table 9. Crude association of diabetic complications during pregnancy and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Table 10. Crude association of gestational diabetes and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Table 11. Log Poisson regression model for estimating the log risk of any hypertensive complications adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data (n=1096)

Table 12. Log Poisson regression model for estimating the log risk of any hypertensive complications adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of white maternal race (n=444)

Table 13. Log Poisson regression model for estimating the log risk of any hypertensive complications adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of black maternal race (n=481)

Table 14. Log Binomial regression model for estimating the log risk of transient hypertension adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data (n=1096)

List of Tables in the Appendices

pregnancies for women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011 (n=2167)

Chapter 1. Literature Review

I. Introduction

In many developed nations and some developing countries, postponement of parenthood is becoming an increasing trend. The average age of first birth in many European countries is now between the ages of 28 and 29, an increase from 25 years since the 1970s (1). In the United States, the proportion of women who are 35 years or older among all women giving birth to their first child, rose from one in 100 in 1970 to one in 12 in 2006, and this trend has been particularly evident among women with higher education (2, 3). Various other reasons have been raised to account for this trend, including the availability of contraceptive pills and reproductive technologies, rise in female employment, changes in cultural norms concerning marriage, and financial difficulties of young adults (1). In addition to the economic and occupational advantages in having children later in life, postponing parenthood also increases the chances of raising children in more stable childbearing environments within more stable parental relationships who experience less parenting stress (4).

However, delaying childbearing has negative obstetrical consequences. Epidemiologic studies have shown that fecundability (probability of conceiving) and fertility (live birth rates) decrease with maternal age (4, 5), while risk of miscarriage increases significantly among mothers of ages 35 and older (6). Even after successful conception and pregnancy through term, advanced maternal age has been known to be associated with various adverse pregnancy outcomes. Advanced maternal age of over 40 years old at the time of delivery has been shown to result in increased risk for intrauterine growth restriction (7, 8), cesarean delivery (9-11), and congenital anomalies, most notably chromosomal disorders such as Down syndrome (Trisomy 21) compared to younger mothers aged 20 to 29 years (4, 12). Though the trend has not been clearly demonstrated in hospital-based studies, advanced maternal age of over 40 years old has

also been associated with increased risk of prenatal mortality and stillbirth in population-based studies (13-15).

Pregnancy at an advanced maternal age also increases the chances of developing complications during pregnancy, and epidemiological studies have suggested that risk of hypertensive and diabetic complications increase with maternal age, since prevalence of pre-existing hypertension and diabetes also increase with age (16-18).

Hypertensive disorders complicate 10% of all pregnancies, and are the second leading cause of maternal death in developed countries, next to direct causes of death such as complications from anesthesia and cesarean sections, and accounts for 16.1% of total maternal deaths (19, 20). In Latin America and the Caribbean, the prevalence of hypertensive complications during pregnancy is estimated to be 25.7%, which makes it the leading cause of maternal morbidity in these countries (20). In developing countries, poor management of hypertension, preeclampsia and eclampsia is one of the major causes of maternal mortality and stillbirth (21, 22). Chronic hypertension alone increases the risk for preterm birth, low birth weight (LBW) infants, and small for gestational age (SGA) infants compared to normotensive women (23, 24). Development of preeclampsia can lead to life-threatening complications such as respiratory distress syndrome and intrauterine growth restriction (25). Gestational diabetes has been known to increase the risk for spontaneous abortion, stillbirth, macrosomia and shoulder dystocia, malformation, neonatal hypoglycaemia, and infant respiratory distress syndrome in the infant. For the mother, gestational diabetes increases the risk for pregnancy-induced hypertension, preeclampsia, post-partum haemorrhage, infections, prolonged labor, and even the chances of developing type-2 diabetes in the future (26).

Due to these adverse consequences, understanding the risk factors associated with hypertensive and diabetic complications during pregnancy is invaluable for the proper management of risk and control of these conditions. As aforementioned, it is generally understood that chronic hypertension and chronic diabetes tend to increase with maternal age.

However, study results are inconsistent when the relationship between advanced maternal age and specific pregnancy hypertensive and diabetic complications are studied. Hypertensive and diabetic complications of pregnancies are a conglomeration of disorders, and the inconsistency in the specific complication measured, and which criteria were used for the diagnosis, may have influenced the study outcomes.

Hypertensive complications during pregnancy are divided into four categories: chronic (or pre-existing) hypertension, transient (or gestational or pregnancy-induced) hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension. Generally, if hypertension (blood pressure ≥ 140/90mmHg confirmed on two separate occasions) is present before 20 weeks of gestation or persists more than 12 weeks postpartum, the patient is diagnosed as having chronic hypertension. If hypertension develops after 20 weeks of gestation, but resolves within 12 weeks postpartum, the patient is diagnosed with transient (pregnancy-induced) hypertension. De novo hypertension beyond 20 weeks gestation with significant proteinuria is diagnosed as preeclampsia, and eclampsia is diagnosed when seizures develop in addition to preeclampsia although eclampsia may develop rapidly without signs of preeclampsia (25, 27, 28). Some studies have investigated the risk of all hypertensive disorders together, while others have combined chronic and transient hypertension together. It is possible that certain type of hypertensive complications is more susceptible to age, while others are less so.

Diagnostic criteria for gestational diabetes is even further complicated, as choice of diagnostic criteria differ by study location and when the study was conducted. This is because there is no consensus as to which screening and diagnosis criteria lead to best clinical advantages over the cost of over-testing and over-diagnosing mothers that may not develop any adverse obstetrical outcomes (29).

Gestational diabetes has traditionally referred to cases where patients without any previous history of diabetes are found to have glucose intolerance during pregnancy. This includes women who are diagnosed with unrecognized, chronic diabetes mellitus for the first time

during pregnancy, as well as those who develop glucose intolerance during pregnancy, and those whose glucose intolerance persisted after delivery. In the US, guidelines from the American Congress of Obstetricians and Gynecologists (ACOG), which recommend the use of Carpenter & Coustan or National Diabetes Data Group (NDDG), and the American Diabetes Association (ADA) are most often used. The National Institute for Health and Clinical Excellence (NICE) is used in the United Kingdom. The World Health Organization criterion is commonly used in countries outside of North America (30). The International Association of Diabetes and Pregnancy Study Group (IADPSG) guidelines are used in Germany and Japan. Therefore, the prevalence of gestational diabetes will differ greatly depending on the screening method and the diagnostic criteria used (31). This may partially explain why the prevalence of gestational diabetes reported in literature ranges widely from 1.7% to 11.6% even within high-income countries (32).

There are also ambiguities as to whether advanced maternal age itself increases the risk for hypertensive and diabetic complications, or we are observing the effects of other risk factors that are also associated with age. Accurate information on risk factors such as maternal race/ethnicity, obesity, socioeconomic status, family medical history, pre-existing medical conditions, and use of assisted reproductive technologies (ART) are lacking in may studies, and even when studies have this information, not all studies considers them in their analysis.

The prevalence of hypertensive disorders among pregnant women differs by age, geographical location, and race/ethnicity. In the US, the prevalence of chronic hypertension for women in their 30s is about 5.4% for non-Hispanic white women, but is more than doubled (14.5%) for non-Hispanic black women. For women in their forties, the prevalence of chronic hypertension is 19.9% for non-Hispanic white women, and 45% for non-Hispanic black women (33). A population-based epidemiological study from the US by Wallis et al. showed that the risk of preeclampsia is 34.1 per 1000 deliveries in the South compared to 29.3 per 1000 deliveries in the Northeast. Wallis et al. speculate that this difference in risk was possibly due to higher rates

of obesity among the African-American population, and higher proportion of African-American women in the South (34). Therefore, maternal race and

Other known risk factors for transient hypertension besides race, geographical location, and ethnicity are obesity, previous history or family history of transient hypertension/preeclampsia, multiple gestations, and pre-existing medical conditions, such as kidney disorders and immune disorders (35, 36). Other metabolic disorders that alter insulin resistance such as gestational diabetes, polycystic ovary syndrome, and excessive weight gain during pregnancy have also been known to be associated with increased risk of transient hypertension. Researchers suggest that transient hypertension may be a part of a spectrum of insulin resistance syndrome (37-39).

Risk factors for preeclampsia are history of preeclampsia in previous pregnancies, family history of preeclampsia, obesity, nulliparity, multiple gestations, change of paternal gametes between pregnancies, and use of donor gametes. Specific pre-existing medical conditions such as renal diseases, pre-gestational diabetes, vascular and connective tissue diseases, autoimmune diseases, and antiphospholipid antibody syndrome have also been known to be associated with preeclampsia (40-43, 19). Although results are not conclusive, very young or very advanced age, ethnicity (African-American and Filipino), and lower socioeconomic status have also been reported to be associated with higher risk for preeclampsia (44, 45). Pregnant women with chronic hypertension are specifically at higher risk for developing preeclampsia. They are referred to as "preeclampsia superimposed on chronic hypertension," and 20 to 25% of women with chronic hypertension develop this condition when hypertension is left unmanaged. Some of the risk factors that have been found to be associated with eclampsia are nulliparity, extremely young or old maternal age, obesity, and low socioeconomic status (46).

Known risk factors for gestational diabetes are obesity, polycystic ovary syndrome, previous history of gestational diabetes, family history of type-2 diabetes, ethnicity, and advanced maternal age (29). A new study by Wang et al., have also suggested that assisted-reproductive

technology may also be associated with increased risk for gestational diabetes (47). Although some studies suggest that gestational hypertension and preeclampsia during pregnancy may increase the changes of developing chronic diabetes in the future, the influence of transient hypertension on gestational diabetes is not known (48). Studies vary whether these potential confounders have been adjusted for in their studies, which may account for the inconsistency in outcomes across studies.

The third reason for the inconsistency in study outcomes may be related to the choice of the age groups. The definition of advanced age and the selection of reference group vary across studies, making the interpretation of outcomes across studies a challenging process. Some studies have used maternal age of 35 or older as the advanced maternal age group, while others have used over 40 or 45. There are studies that have used women in the 20s as the reference group (49, 50), while others have used a much older reference group (51, 52).

These inconsistencies may account for the differences in outcomes of studies investigating the effects of advanced maternal age on hypertensive and diabetic pregnancy complications. A detailed comparison of study design and analysis, with particular attention to the specific hypertensive complications that was studied, the selection of advanced maternal age group, and choice of confounders adjusted for, may be beneficial in understanding whether advanced maternal age alone may be an independent risk factor for hypertensive and diabetic complications during pregnancy.

Therefore, the purpose of this paper is two-fold: 1) to review current literature on the effects of advanced maternal age on hypertensive and diabetic complications of pregnancy among studies that also provide data on the prevalence of chronic hypertension and diabetes, and other potential risk factors such as race/ethnicity, smoking status, socioeconomic status, obesity, and pre-existing medical conditions, and 2) to consider how study design, choice of advanced age group and reference group, choice of analysis methods and outcomes may have influenced their results.

II. Methods

Using 3 electronic medical databases MEDLINE, Web of Science, and Google Scholar, literature search was conducted in March 2013 using the keyword "advanced maternal age" or "maternal age" with "pregnancy complications," "transient hypertension," "preeclampsia," "eclampsia," or "gestational diabetes" to identify publications between 1990 to 2013. Population-level studies and hospital-base studied, as well as studies from high, middle, and lower-income countries were included. Publications that were not in English were excluded from the review. Each article was reviewed by hand to detect whether the study contained data on effects of advanced maternal age on hypertensive and diabetic complications during pregnancy, which included any of the following pregnancy complications: transient hypertension, mild preeclampsia, severe preeclampsia, eclampsia, and gestational diabetes. Studies that did not report on the prevalence of pre-pregnancy hypertension and diabetes were excluded from the study. Data on other potential risk factors for hypertension and diabetes such as race/ethnicity, education, occupation, obesity, and pre-existing medical conditions such as cardiac diseases, thyroid disorders and metabolic disorders were extracted from the studies. Information on parity and the use of ART or *in vitro* fertilization (IVF) among the study population were also extracted. Studies were categorized according to how advanced maternal age was categorized in the study. If more the study had more than two age categories, they were categorized according to their oldest age group. Studies enrolling only

III. Findings

Study design, size, and demographic characteristics

A total of 39 studies were obtained and categorized according to their highest age group used for advanced maternal age (Table 1). Of the 39 publications, 22 studies were retrospective single center hospital-based cohort studies, twelve were large multicenter studies or retrospective population-based cohort studies using regional birth registries and health databases, and five were

prospective single center hospital-based cohort studies (52-56). Additionally, there was one retrospective multicenter cohort study (50), one case-control study (57), and one prospective multi-center cohort study (16). There were 14 publications from the Middle East including six studies from Israel, nine studies from North America, eight publications from Europe, four studies from Asia, three from Australia, and one from Africa.

Among all 37 studies, 21 studies enrolled patients according to birth, and 16 studies enrolled patients according to conception after 10 to 24 weeks of gestation (16 studies). There were 18 studies that either restricted patient enrollment by nulliparous pregnancies or stratified their results by nulliparous and multiparous women, whereby adjusting for parity in their study, and 12 studies that adjusted for multiple births in their analyses by enrolling only singleton births or pregnancies. Almost all studies had information on parity or gravidity of the cohort.

Patient demographics such as race, education, marital status, smoking status, obesity, were reported in mostly population-based cohort studies, but less frequently in hospital-based cohort studies. Some hospital-based cohort studies reported on demographic characteristics such as occupation, marital status, and ethnic background (51, 53, 58, 59), but most hospital-based studies did not provide any demographic information. Because all population-based cohort studies were from Europe, North America, Australia, they appeared to have a high proportion of white mothers in the cohort, ranging from 69.4% (60) to over 93.1% (27) in the advanced maternal age group, although distribution of race was not reported in many studies from Europe. Three studies from the US had the most ethnically diverse cohort. In these studies, there were significantly higher proportion of Whites and Asians in the advanced maternal age group, whereas younger mothers tended to have higher proportion of Hispanics. In comparison, the distribution of blacks was more consistent across different age categories. All three studies adjusted for race in their analysis.

Pre-existing medical conditions

Studies revealed varying prevalence of chronic hypertension within their study population. This discrepancy was probably due to how chronic hypertension was screened and diagnosed in these studies. For instance, Jolly et al. reported that they counted those who had chronic hypertension when mothers booked their first prenatal care visits, whereas other studies used ICD-9 diagnosis codes to pull records for chronic hypertension retrospectively from electronic medical charts. Only one study screened patients prospectively and diagnose them using international guidelines (International Society for the Study of Hypertension in Pregnancy). This study reported that the prevalence of chronic hypertension was 0.1% in the younger reference group (20-29 years old), and 0.8% in the advanced age group (30-39 years old) (57). In most studies, the prevalence of chronic hypertension generally ranges from 0% to 2.0% in the younger age group (62, 63), but the study by Jolly et al. (60) reported 4.7% in the younger age group (18 to 34 years old). In the advanced maternal age group, prevalence of chronic hypertension appeared to range more widely, from 0.6% to 0.8% (61), to as high as 10.1% to 13% (64, 65).

Most studies reported prevalence of pre-existing diabetes in their study population to be below 2%. Studies with the highest prevalence of chronic diabetes were from Israel: 4.5% (66) and 9.6% (55) in the advanced maternal age group of over 45 years old. This is not surprising, as prevalence of chronic diabetes is known to be high in Middle Eastern countries (67).

Despite this variability in prevalence of chronic hypertension and diabetes, most studies reported that prevalence was significantly association with maternal age. Out of 22 studies that had a statistical test for whether or not risk for chronic hypertension was higher in the advanced age group, 16 studies found significant increase in the advanced maternal age group, and two studies reported significant difference in risk for multiparous mothers, but insignificant difference in risk for nulliparous mothers (68, 9). Out of 17 studies that had a statistical test for whether or

not risk for chronic diabetes was higher in the advanced age group, 11 studies found significant increase in the advanced maternal age group, but six studies reported insignificant outcomes.

Studies varied in how other pre-existing conditions were reported. Although most studies reported chronic (also referred to as pre-existing or essential) hypertension and pre-existing (pre-gestational) diabetes separately from transient hypertension and gestational diabetes, some studies reported the combined effects as hypertensive complications or diabetic complications. All six of these studies found significant association between hypertensive and diabetic complications and advanced maternal age, but this is expected, as rates of chronic hypertension and chronic diabetes are known to increase with age.

Many studies grouped various pre-existing medical conditions together (e.g. thyroid dysfunctions, anemia, asthma, cardiac diseases, renal diseases, immune disorders, seizures, neurologic disorders, psychiatric disorders, and genetic abnormalities), and report them as concurrent diseases, medical disorders, or chronic conditions. However, only five studies adjusted for these conditions in their analysis (9, 13, 16, 18, 69), and two studies adjusted for pre-existing medical conditions by enrolling only those without any chronic conditions in their study (56, 59).

Over 35 years old as the advanced maternal age group

There were eight studies that used 35 years old as a cut-off age for advanced maternal age (Table 1). Among these studies, three studies used ages 35 or younger, or below 35, as the comparison group (58, 70, 71), three studies used 29 or younger as the comparison age group (49, 50, 72), and two studies used 25 or younger as the comparison age group (62, 65).

Studies that used a much younger comparison group tended to be small retrospective studies, but there was no obvious trend between study size and study outcomes. Amongst the seven studies that used a cut-off age of 35 years for advance maternal age to investigate the risk

of preeclampsia, three studies found significant increase in risk in the advanced maternal age group (70-72), but three studies did not find a statistically significant association (49, 58, 62).

Study by Biro et al. (71) was the only retrospective population cohort study in this age group that had reported pregnancy-induced hypertension (transient hypertension), preeclampsia/HELLP syndrome, and gestational diabetes. The study adjusted for parity and public or private hospital admission status, and found significant association between transient hypertension, preeclampsia/HELLP syndrome, and gestational diabetes with advanced maternal age.

Interestingly, Shehadeh's study (65) was the only study that had separately reported preeclampsia without history of chronic hypertension from superimposed preeclampsia, and demonstrated that risk for chronic hypertension and superimposed preeclampsia were both higher among the older age group, but preeclampsia without history of chronic hypertension was higher in the younger reference group. Shehadeh's study was also unique in that the reference group more than 10 years younger than the advanced age group. Because young maternal age has also been known to be associated with preeclampsia, the effects of advanced maternal age may not have been as evident in studies where young comparison group in their 20s were used.

Over 40 years old as the advanced maternal age group

There were 19 studies that used 40 years old as a cut-off for advanced maternal age (Table 2). Among these, ten studies used a reference group that included only women in the 20s (9, 18, 54, 57, 68, 73-76), and seven studies used women who are below 35 as the reference group (16, 60, 64, 77-80). Only two studies had a comparison group of women who were below 40 (47, 63).

Wang et al. (61) used a reference age group of 35 to 39, whereas Chan and Lao used all ages below 40 as the reference group to investigate whether there were significant increases in risk for preeclampsia and gestational diabetes in the advanced maternal age group. Wang's study

resulted in insignificant outcome, whereas Chan and Lao's study (63) showed significant increase in risk in the advanced age group. Although other factors such as sample size, prevalence of obesity, and maternal race (Norwegian and Asian) may have caused the observed difference in outcomes, the choice of the reference group may also have been a contributing factor.

Over 45 years old as the advanced maternal age group

There were six studies that used 45 as a cut-off value (Table 3). Four of these studies used women of ages 20 to 29 as a reference age group (10, 13, 55, 66), one study used a reference group of 30 to 34 years of age (17), and one used 40 and under as the reference group (81).

Spontaneous pregnancies are rare among women beyond 45. Women who deliver after 45 tend to be those who have very high gravidity and parity, and lower rates of spontaneous abortion compared to nulliparous women (82, 83). As observed in the study by Dulitzki et al. (10), there were significant differences in the proportion of those who used assisted conception (6.5% in the reference group 20 to 29 years old compared to 26.6% in the advanced age group) and egg donation (0% in the reference group compared to 13.7% in the advanced age group).

Amongst the six studies, only Laskov et al. (81) adjusted for the use of ART by enrolling only women who conceived through *in vitro* fertilization (IVF). Laskov et al. found significant increase in risk for transient hypertension, severe preeclampsia, and gestational diabetes in the advanced age group (≥45 years old) compared to the reference group (<40 years old). However, only the use of ART and multiple births were adjusted for in this study. Nulliparity is also an important risk factor for hypertensive complications during pregnancies. Only Luke and Brown (17) adjusted for this among the six studies, and demonstrated that hypertensive and diabetic complications increase with maternal age after adjusting for maternal race and parity. No study adjusted for both the use of assisted conception and parity. Studies enrolling women who are over the age of 45 should consider providing stratified results for nulliparous and multiparous women, and controlling for the use of ART.

Over 50 years old as the advanced maternal age group

There were five studies that used age 50 as a cut-off value to investigate the effects of advanced maternal age on pregnancy complications, and all of these were single hospital studies (51, 52, 56, 59, 84) (Table 4). Amongst all women in these studies, only two mothers who are 50 and over conceived spontaneously (59). All other women conceived through the use of IVF technologies using oocyte donations. Two of the five studies considered nulliparity as a risk factor for adverse pregnancy complications, and controlled for its effects by either enrolling only nulliparous patients in the study (51), or stratifying the population by parity (59). Only Chibber's study resulted in significant results. Chibber's (59) study found that women of advanced maternal age (≥50 years old) have higher risk of preeclampsia and gestational diabetes, even after adjusting for chronic conditions (including chronic hypertension), race, and parity, but not adjusting for the use of assisted reproductive technology and multiple births. Small sample size may have accounted for non-significant outcomes in other studies in this age category.

Outcome

Similar to pre-existing conditions, studies varied widely on how hypertensive and diabetic complications of pregnancy were reported. Most studies reported on preeclampsia and gestational diabetes, but transient hypertension was reported in fewer studies. Some studies grouped all hypertensive disorders such as transient hypertension, preeclampsia, and eclampsia together, without providing separate results for each (56). Other studies reported on "hypertension" or "hypertensive disorders" without clarifying which specific they were referring to. Not all studies clearly distinguished chronic hypertension, transient hypertension, mild preeclampsia, severe preeclampsia, eclampsia, as well as chronic and gestational diabetes, and few studies also provided information on the diagnostic criteria that was used in the study (13, 16). There were also five studies that grouped pre-existing and gestational diabetes together (17, 62, 70, 74, 80), and two studies reported chronic and transient hypertension together (7, 58).

a. Transient hypertension

Prevalence of transient hypertension in various reference age groups ranged widely from 0.4% (ages 20-25) the study by Amarin and Akasheh (62) to 11% (ages 20-29) in the study by Ludford et al. (76). Study by Glasser et al. (51) reported unusually high prevalence of 36.3% in the reference group, but was explainable by the age range of this group 45 to 49 years old. In the advanced maternal age group, transient hypertension ranged from 1.8% (ages 40-44) in a study by Jacobsson et al. (13) to as high as 18.5% (≥40 years old) in the study by Diejomaoh et al. (74). Cleary-Goldman, et al. (16) used "blood pressure >140/90 on at least 2 occasions greater than 6 hours apart without evidence of chronic hypertension or significant proteinuria" to diagnose chronic hypertension, but most retrospective studies did not indicate how transient hypertension was screened and how they were diagnosed.

Despite this inconsistency, nine out of 15 studies that had a statistical test reported significant difference in risk for transient hypertension in the advanced maternal age group compared to the reference group. Of the six studies that did not find a statistically significant relationship, three were from studies of women of over 50 as the advanced maternal age group with small sample size (51, 52, 84). However, the other three studies that did not find significant results were from population-based cohort studies with large sample sizes (16, 76, 79). There were also three population-based cohort studies that found a statistically significant association between advanced maternal age and transient hypertension (13, 17, 71). Most small cohort studies appear to show that the risk of transient hypertension increases with advanced maternal age, but half of the large population-based cohort studies found insignificant outcomes, and results are not conclusive.

b. Preeclampsia

Fifteen studies out of 25 studies that investigated the difference in risk for preeclampsia in the advanced maternal age group compared to the younger reference group found a significant

increase in risk in the advanced age group, and two studies presented different results stratified by parity.

Abu-Heija et al. (66) used a much younger reference group (age 20-29) compared to the advanced age group (age ≥ 45), and report significant difference in the incidence of preeclampsia between these two age groups (1.6% in the reference group versus 12.3% in the advanced age group). However, choice of very young reference group did not always result in significant outcomes. A study by Jacobsson et al., which used data from the Swedish Birth Registry, reported that risk for severe preeclampsia was higher in the older age group (0.66% in age group ≥45) compared to the younger reference group (2.1% in ages 20-29), but risk for severe preeclampsia was actually higher among the younger age group (13). There were three other studies that reported outcomes for mild and severe preeclampsia separately (59, 64, 84), and two studies by Chibber (59) and Yaniv et al. (64) found significant increase in risks for both mild and severe preeclampsia in the advanced maternal age group. It is possible that mild preeclampsia and severe preeclampsia have different profiles of risk factors, and the effects of age on the risk for these two conditions also differ.

Nullparity is a known risk factor for preeclampsia. Some studies that stratified its outcomes by nulliparous and multiparous women found significant association between age and preeclampsia in both strata (9, 59, 63, 71, 75), and two studies did not find significance in either nulliparous or multiparous women (47, 49). One study found significant association between advanced maternal age and preeclampsia in multiparous women, but not in nulliparous women (68). Studies that only recruited nulliparous women also had both significant and non-significant outcomes.

Therefore, maternal age, along with how advanced maternal age was categorized, or how the younger reference group was selected, do not appear to determine the risk for preeclampsia. Parity may play a larger role in the development of preeclampsia, but effects of parity or its

interaction with age on the risk for preeclampsia is outside the scope of this review. Results regarding effects of advanced maternal age on preeclampsia are not conclusive.

c. Eclampsia

Only four studies provided any information on eclampsia – one study reported on eclampsia separately from preeclampsia (62); one study reported on risk of developing eclampsia among preeclampsia patients (70); and two studies reported on eclampsia grouped together with preeclampsia (56, 79). Only Kullmer et al. (79) reported significant increase in the risk of preeclampsia/eclampsia in the advanced maternal age group.

d. Gestational diabetes

Studies varied in how gestational diabetes was diagnosed. Study by Jahromi et al. (57) counted any patients with abnormal fasting glucose and abnormal glucose tolerance test as having "diabetic complications," whereas other studies followed diagnosis such as Carpenter and Coustan criteria (55), or modified version of Carpenter and Coustan criteria (16). Two studies reported gestational diabetes as GDM-A1 (diet controlled) or GDM-A2 (insulin-requiring) (64, 84). Most retrospective cohort studies did not clarify how gestational diabetes was diagnosed and classified at the time of diagnosis.

This inconsistency in diagnostic methods may account for the wide range in the prevalence of gestational diabetes observed in the study population. Gestational diabetes ranged from 0.28% in the 20-29 reference age group by Jacobsson et al. (13) to as high as 10.2% and 13.4% reported in studies from Laskov et al. (81) and AlShami et al. (58) in the under 40 and 20-34 reference age group. In the advanced age group, Chan and Lao (63) reported that they found risks of developing gestational diabetes as high as 25% of nulliparous women and 31% of multiparous women in their study over 40 years of age in their study. Roughly a third of their study population had obesity, which may explain the unusually high risk of gestational diabetes in this study.

Twenty-seven studies in this review reported on gestational diabetes, and twenty of these found statistically significant increase in risk of gestational diabetes in the advanced maternal age group compared to the younger reference group. All population-based cohort studies that measured the risk for gestational diabetes reported significant association. Seven studies did not find significant association between gestational diabetes and advanced maternal age. The cut-off age in these studies were 35, 40, or 45, and these cut-offs did not seem to influence whether a study resulted in significant or insignificant outcomes. There were six studies that grouped pre-existing and gestational diabetes together, and reported the risk for having either of the two conditions (7, 17, 62, 70, 74, 80). All of these studies found that risk for pre-existing and gestational diabetes was significantly higher in the advanced maternal age group compared to the younger reference group. One study provided data on "Diabetes Mellitus," but did not specify whether or not gestational diabetes were included (66). Many studies demonstrate an age associated increase in risk of gestational diabetes, and the results of this review are consistent with what has been previously known.

Results of population-based cohort studies

All large multicenter studies or population-based cohort studies were from high-income countries, which included five studies from Europe, four from North America, and three from Australia. Five studies that reported on the prevalence of chronic hypertension all found significant increase in the prevalence in the AMA group (16, 17, 70, 75, 76). Three studies out of six that reported on transient hypertension did not find a statistically significant increase in transient hypertension in the advanced maternal age group (16, 76, 79). Ludford et al. (76) and Cleary-Goldman et al. (16) reported incremental rise in risk of chronic hypertension with increasing maternal age, but did not find this association for transient hypertension. Three studies showed a statistically significant increase in risk for both chronic and transient hypertension in the AMA group (7, 13, 17).

Of the nine studies that reported on preeclampsia (and or eclampsia), five studies found statistically significant increase in risk for preeclampsia in the advanced maternal age group, two studies did not find a statistically significant increase (16, 62), one study did not report a statistical test, and one study by Jacobsson et al. reported mixed outcomes (13). Using the Swedish Medical Birth Register, Jacobsson et al. (13) found that mild preeclampsia was more likely to occur in the younger group (age 20 to 29) compared to the advanced maternal age group (age ≥45), but severe preeclampsia was more likely to occur in the advanced age group compared to the younger group. Of the two studies that did not find a significant increase in risk of preeclampsia in the AMA group, the study by Jolly et al. (60) adjusted for chronic diabetes, gestational diabetes, and smoking

Of the six studies that reported on the prevalence of chronic diabetes, three studies reported age-associated increase in prevalence (17, 69, 79), and three studies did not find difference in the prevalence across age groups (13, 16, 76). Amongst the ten large multicenter or population-based studies that reported on gestational diabetes, six studies reported significantly higher risk of gestational diabetes in the advanced maternal age group, three studies reported increase in combined risk for chronic and gestational diabetes, and one study did not report a statistical test but showed increase in risk for gestational diabetes.

Amongst all large population-based studies, only two studies adjusted for pre-existing medical conditions and other important risk factors such as maternal race and parity in their study. A study by Jacobsson et al. (13) adjusted for parity, marital status, smoking status, multiple gestations, malformations, and pre-existing maternal diseases, which included hypertensive diseases, diabetes, bronchial asthma, disseminated lupus erythematosus, and inflammatory bowel disease. He found that AMA increased the risk of transient hypertension, severe preeclampsia, and gestational diabetes, but not mild preeclampsia. Cleary-Goldman et al. (16) adjusted for study site, maternal race, parity, BMI, education, marital status, smoking status, previous adverse pregnancy outcome, use of assisted conception, and pre-existing medical

conditions in his study. Pre-existing medical conditions included were pre-gestational diabetes, cardiac disease, chronic hypertension, renal disease, thyroid disease, autoimmune disease, seizure disorders, neurologic disorders, psychiatric disorders, and genetic abnormalities (maternal or paternal). He found that AMA increased the risk of gestational diabetes, but not transient hypertension or preeclampsia.

IV. Discussion

This study attempted to review literature on advanced maternal age and its effects on risks for hypertensive and diabetic complications during pregnancy. Studies that have reported the prevalence of pre-existing conditions of their study sample, including pre-existing hypertension and diabetes, were selected. Studies were compared according to study size, choice of advanced age group and reference age group, study outcomes, and choice of confounders adjusted for in their study, such as race/ethnicity and parity.

Thirty-nine studies were collected, and among these were twelve large population-based cohort studies. Majority of the studies reported significant increase in risks for chronic diabetes and gestational diabetes in the advanced maternal age group. Risk for preeclampsia was also significantly increased in older age groups compared to younger reference groups in most studies. The choice of reference group and advanced maternal age group did not appear to influence study outcomes. However, transient hypertension and eclampsia were not investigated in many studies, and the influence of advance maternal age on these conditions remains uncertain. Population-based cohort study using the Swedish Birth Registry by Jacobsson et al. (13) showed that risk of mild preeclampsia was higher in the younger reference group (20-29 years old) compared to the advanced age group (≥45 years old), but risk for severe preeclampsia was higher in the advanced age group compared to the reference group. Whether or not the effects of maternal age are different for mild and severe preeclampsia, is also undetermined.

Not all large population-based cohort studies reported consistent outcomes. Although all studies reported increase in chronic hypertension and gestational diabetes in the AMA group, conflicting results were found for transient hypertension and preeclampsia. Small cohort studies that defined advanced maternal age group as 50 years or older tended to have insignificant outcomes due to their small sample size, whereas other small cohort studies showed statistically significant outcomes.

Although many studies had significant differences in maternal race and prevalence of obesity across age groups, most studies did not adjust for these factors in their analyses. There were only two small cohort studies (9, 18) and two large population-based studies (13, 16) that adjusted for chronic conditions. All four of these studies found significant association of AMA and gestational diabetes, but results were not consistent for transient hypertension and preeclampsia.

Limitations

Limitation of this study is the variability in the characteristics of the study population, study design, and screening and criteria used for diagnosing hypertensive and diabetic complications during pregnancies, which make comparison of studies difficult. Although many studies took parity and multiple births into consideration, most studies did not adjust for the history of medical conditions, parity, and use of ART in their results, as these are often difficult to obtain in retrospective studies. This review also did not provide effect measure calculations (meta-analysis) that summarize data from all studies. Additionally, large, population-based cohort studies tended to have greater proportion of white, affluent, and well-educated women in their study population compared to the general US population. Evidence of other ethnic groups or middle and low-income countries, and evidence from ethnically diverse populations in high-income countries are lacking. These limitations make generalizability of findings difficult, and assessing the sole impact of age on pregnancy complications remains a challenge.

Conclusion

Despite variations in study size, study location, choice of AMA and reference groups, studies in this review showed that women who conceive at an advanced age (≥35 years old) have higher risk of chronic hypertension and gestational diabetes, but the effects of AMA on the risks of transient hypertension, mild preeclampsia, and severe preeclampsia separately, are unclear.

In the US, the incidence of transient (gestational) hypertension and preeclampsia have been increasing due to increase in prevalence of known risk factors such as chronic hypertension, pre-gestational diabetes, and obesity, although overall maternal morbidity has remained the same in the last several decades (34, 85). Transient hypertension affects about 6% to 7% of pregnancies, while preeclampsia complicates about 2% to 8% of pregnancies (86). Therefore, future studies should aim to explain how important age is as a risk factor for these conditions, and how it is related to other known risk factors.

As more women delay childbearing, there is greater need for empirical evidence regarding risks of advanced age on maternal and child outcomes for both patients and health practitioners. It is essential for health care providers to have such information to better counsel patients who wish to become pregnant at an older age, and for patients to better understand the benefit and risks of delaying childbearing when planning their pregnancies. With such evidence, physicians may be able to more closely monitor higher risk women. Additionally, they may help increase patients' awareness of the types of complications they may experience, and suggest other lifestyle changes that may help them avoid adverse pregnancy outcomes.

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Table 1. Studies using 35 years of age as the cut-off value for the advanced maternal age group (n=9)

Author	Country Year	Title	Study design	Age Groups: Sample Size	Enrollment Criteria	Nulliparous	ART	Characteristics	Pre-existing Conditions	Outcomes
Lamminpaa et al.	Finland 2012	Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997-2008	Retrospective population based cohort study (3 Finnish Health Registries)	1) <35: 15437 2) ≥35: 2387	Singleton pregnancies with preeclampsia	100%	1.9% vs 7.7% (IVF)	Smoking: 14.2% vs 9.5%* Unmarried: 47.6% vs 47.3% (NS) BMI>25: 41.6% vs 56.2%*	Chronic HTN: 1.1% vs 2.1%* Anemia: 0.6% vs 0.6% (NS)	Preeclampsia: 6.4% vs 9.4% (N/A) Preexisting and gestational DM: 4.9% vs 9.3%*
Biro et al.	Australia 2012	Advanced maternal age and obstetric morbidity for women giving birth in Victoria, Australia: A population-based study	Retrospective population based cohort study (Victorian Perinatal Data Collection)	1) < 35: 48273 2) ≥ 35: 9153 1) < 35: 53065 2) ≥ 35: 22866	≥ 20 wks	100% 0%	N/A	Married: 71.4% Born in Australia: 75.4% Born in Asia: 10.2% Hospital admission (public): 63.8%	Chronic HTN: 1.1% Preexisting DM: 0.5%	Pregnancy-induced hypertension: 8.4% vs 9.4%* (cOR1.12[1.04-1.21], aOR1.17[1.08,1.26]) Preeclampsia/HELLP: 4.4% vs 5.3%* (cOR1.23[1.11,1.37], aOR1.24[1.11,1.37]) Gestational DM: 4.1% vs 6.8%* (cOR1.70[1.55,1.86], aOR1.83[1.67,2.02]) Pregnancy-induced hypertension: 3.6% vs 4.1%* (cOR1.17[1.08, 1.26], aOR1.25[1.15, 1.35]) Preeclampsia/HELLP: 1.3% vs 1.6%* (cOR1.24[1.09,1.40], aOR1.29[1.14,1.47]) Gestational DM: 4.1% vs 7.2%* (cOR1.80[1.69,1.92], aOR2.01[1.88,2.15])
AlShami et al.	UAE 2011	Pregnancy outcome in late maternal age in a high-income developing country	Retrospective cohort study (1 hospital)	1) 20-34: 699 2) ≥ 35: 189	All births	32.3% vs 3.2%	N/A	Arabs: 44.6% vs 49.2% (NS) Indian: 21.8% vs 19.5% (NS)	Chronic or Gestational HTN or preeclampsia: 5.1% vs 7.4% (NS) Preexisting or Gestational DM: 13.4% vs 28.5%* Anemia: 57.2% vs 48.3% (NS)	
Borowski and Bottoms	US 1995	Underappreciated risks of the elderly multipara	Retrospective cohort study (1 hospital)	1) 20-29: 2092 2) ≥35: 170 1) 20-29: 5460 2) ≥35: 1024	Singleton pregnancies >500g and >20 wks	100% 0%	N/A	Black: 78.9% vs 41.1% (N/A) Married: 26.7% vs 68.2% (N/A) Tobacco: 22.1% vs 17.6% (N/A) Alcohol: 4.1% vs 4.7%* Obesity: 8.8% vs 12.4%* Black: 83.2% vs 72.7% (N/A) Married: 29.6% vs 50.0% (N/A) Tobacco: 30.1% vs 32.2% (N/A) Alcohol: 6.4% vs 10.4%* Obesity: 9.2% vs 15.5%*	Chronic HTN: 1.4% vs 3.5%* Chronic HTN: 0.5% vs 2.8%*	Preeclampsia: 7.9% vs 8.8% (NS) Severe eclampsia: 0.8% vs 0.6% (NS) Gestaional diabetes: 2.7% vs 5.3%* Clinical diabetes: 2.1% vs 4.1%* Preeclampsia: 2.3% vs 6.3% (NS) Severe preeclampsia: 03% vs 1.3% (NS) Gestational DM: 1.9% vs 8.5%* Clinical diabetes: 1.1% vs 3.5%*
Prysak et al.	US 1995	Pregnancy outcome in nulliparous women 35 years and older	Retrospective cohort study (3 Hospitals)	1) 25-29: 1054 2) ≥ 35: 890	Singleton Births	100%	N/A	White: 95% vs 94% (NS) Married 94% vs 92%* Private insurance: 95% vs 97%* Smoker: 15.8% vs 14.2% (NS) Obesity (>200lb): 3.2% vs 6.9%*	Chronic HTN: 0.8% vs 2.7%* Preexisting DM: 0.6% vs 0.7% (NS) Asthma: 0.5% vs 1.3%* Leiomyomas: 0.8% vs 3.7%*	Transient HTN: 8.3% vs 14.3%* Gestational DM: 0.8% vs 1.1% (NS) Gestational DM without insulin: 2.8% vs 6.9%*
Delbaere et al.	Belgium 2007	Pregnancy outcome in primiparae of advanced maternal age	Retrospective population based cohort (Flemish Study Centre for Perinatal Epidemiology)	1) 25-29: 23921 2) ≥ 35: 2970	Singleton Births of >500g	N/A	1.6% vs 9.2%	N/A	Chronic HTN and Transient HTN: 6.6% vs 8.7%* Preexisting and gestational DM: 1.1% vs 2.5%*	
Oboro et al.	Nigeria 2006	Pregnancy outcome in nulliparous women aged 35 or older	Retrospective case control study (2 hospitals)	1) 25-29: 487 2) ≥ 35: 481	Singleton Births	100%	N/A	N/A	Chronic DM: 0.4% vs 0.8% (NS) (OR2.0[0.4, 11.1]) Leiomyoma: 2.9% vs 7.5%* (OR2.7[1.5, 5.1])	Preeclampsia: 8.4% vs 13.3%* (OR1.7[1.1, 2.5]) Gestational DM: 0.8% vs 4.0%* (OR5.0[1.7, 14.7])
Amarin and Akasheh	Jordan 2001	Advanced maternal age and pregnancy outcome	Retrospective cohort study (1 hospital)	1) 20-25: 471 2) >35: 73	All births	N/A	N/A	N/A	Essential HTN: 0% vs 11%* Preexisting and gestational DM: 2.6% vs 12.3%*	Transient HTN: 0.4% vs 2.7%* Preeclampsia 4.5% vs 1.4% (NS) Eclampsia: 0.2% vs 0% (NS)
Shehadeh	Jordan 2002	Elderly primigravida and pregnancy outcome	Retrospective cohort with oversized exposed group (2 hospitals)	1) 20-25: 190 2) ≥ 35: 172	Singleton Births	100%	N/A	Elderly and younger primigravida were matched for social class	Chronic HTN: 3% vs 13%*	Preeclampsia without chronic HTN: 20% vs 5.7%* Chronic HTN superimposed preeclampsia: 2.6% vs 8.7%* Diabetes (unspecified): 0.5% vs 2.3% (NS)

ART: Artificial reproductive technology
HTN: Hypertension
DM: Diabetes Mellitus

OR: Odds ratio
aOR: Adjusted odds ratio
N/A: Not available

NS: Not significant compared to reference group
* Significant difference compared to reference group
Reference age groups are the youngest age group for each study

Table 2. Studies using 40 years of age as the cut-off value for the advanced maternal age group (n=19)

Author	Country Year	Title	Study design	Age Groups: Sample size	Enrollment Criteria	Nulliparous	ART	Characteristics	Pre-existing Conditions	Outcomes
Wang et al.	Norway 2011	The impact of advanced maternal age and parity on obstetric and perinatal outcomes in singleton gestations	Retrospective cohort study (1 Hospital)	1) 35-39: 2213 2) ≥ 40: 616	> 24 wks	100%	N/A	N/A	Chronic HTN: 0.5% vs 0.8% (NS) Preexisting DM: 1.4% vs 1.9% (NS) Heart disease: 2.1% vs 1.5% (NS) Renal disease: 0.6% vs 0.6% (NS) Epilepsy: 0.9% vs 0.6% (NS)	Preeclampsia: 6.7% vs 7.3% (NS) Gestational DM: 1.4% vs 1.1% (NS)
				1) 35-39: 2193 2) ≥ 40: 1597		0%			Chronic HTN: 0.4% vs 0.6% (NS) Preexisting DM: 1.3% vs 1.4% (NS) Heart disease: 1.3% vs 2.3%* Renal disease: 0.4% vs 0.8% (NS) Epilepsy: 0.5% vs 0.7% (NS)	Preeclampsia: 3.5% vs 3.9% (NS) Gestational DM: 2.0% vs 2.5% (NS)
Chan and Lao	Hong Kong 2008	Effect of parity and advanced maternal age on obstetric outcome	Retrospective cohort study (2 Hospitals)	1) <40: 8891 2) ≥40: 200	> 24 wks Singleton	100%	N/A	Smokers: 5% vs 2.5% (NS) Obesity (BMI>25): 31.3% vs 28.5%*	Chronic HTN: 0.3% vs 2.0%* Preexisting DM: 0.1% vs 1.0%* Other medical complications (unspecified): 5.3% vs 6.5% (NS)	Preeclampsia: 3.4% vs 8.5%* (cOR2.68[1.61, 4.46]) Gestational DM: 8.9% vs 24.9%* (cOR3.40[2.49, 4.63])
				1) <40: 6230 2) ≥40: 406		0%		Smoker: 3.0% vs 2.0% (NS) Obesity (BMI>25): 27.1% vs 34.2%*	Chronic HTN: 0.4% vs 1.5%* Preexisting DM: 0.1% vs 1.0%* Other medical complications (unspecified): 6.7% vs 8.4% (NS)	Preeclampsia: 2.0% vs 3.4%* (cOR1.76[1.0, 3.09]) Gestational DM: 12.0% vs 31.3%* (cOR3.34[2.70, 4.14])
Cleary-Goldman et al.	US 2005	Impact of maternal age on obstetric outcome	Prospective multicenter cohort study (15 hospitals)	1) <35: 28398 2) 35-39: 6294 3) ≥ 40: 1364	≥ 10 wks	48.5% vs 33% vs 33.1%*	0.6% vs 3.4% vs 11.8%*	Race* White: 65.4% vs 75.8% vs 75.4% Hispanic: 24.7% vs 13.6% vs 13.7% Black: 5.2% vs 4.3% vs 5.7% Married: 76% vs 88.5% vs 85%* BMI (mean): 24.9 vs 25.3 vs 26* Education (years): 14.1 vs 15.3 vs 15.2*	Pregestational DM: 0.9% vs 1.4% vs 1.7%* Chronic HTN: 0.5% vs 1.4% vs 1.6%* Preexisting conditions: 36.1% vs 43.5% vs 51.5%* (Includes cardiac, renal, thyroid, autoimmune diseases, seizures, neurologic, psychiatric disorders, and genetic abnormalities)	Gestational HTN: 4.7% vs 4.1%* vs 5.5% (NS) (aOR0.8 [0.7, 1.20], aOR 1.0[0.8, 1.4]) Preeclampsia 2.4% vs 2.3% vs 3.0% (NS) (aOR 0.9[0.7, 1.2], aOR1.1[0.7,1.6]) Gestational DM: 2.9% vs 5.3%* vs 7.3%* (aOR 1.8 [1.5, 2.1], aOR2.4[1.9, 3.1])
Yaniv et al.	Israel 2011	A significant linear association exists between advanced maternal age and adverse perinatal outcome	Retrospective cohort study (Single center)	1) <35: 43809 2) 35-40: 1036 3) >40: 188	Singleton Births	100%	4.1% vs 22.6% vs 40.4%*	N/A	Chronic HTN: 1.1% vs 6.0% vs 10.1%*	Mild preeclampsia: 5.7% vs 7.1% vs 10.6%* Severe preeclampsia: 1.9% vs 4.2% vs 4.8%* GDM-A1: 4% vs 15.6% vs 23.9%* GDM-A2: 0.6% vs 4.7% vs 6.4%*
Hoffman et al.	US 2007	Pregnancy at or beyond age 40 years is associated with an increased risk of fetal death and other adverse outcomes	Retrospective cohort study (Single center)	1) <35: 108547 2) 35-40: 13902 3) >40: 3953	Singleton pregnancies	2.0 vs 4.0 vs 4.0 (gravidity)	N/A	Hispanic: 37.6% vs 40%* vs 37.4%* Black: 40.3% vs 38.6%* vs 42.8%* White: 19.5% vs 17%* vs 16.1%*	Chronic HTN: 3.0% vs 6.7%* vs 11.1%* Pregestational DM: 0.7% vs 1.6%* vs 2.2%*	Gestaional DM: 2.4% vs 6.9%* vs 8.7%* Preeclampsia: 6.9% vs 7.4%* vs 9.3%*
Hsieh et al.	Taiwan 2010	Advanced maternal age and adverse perinatal outcomes in an Asian population	Retrospective cohort study (1 hospital)	1) 20-34: 33881 2) 35-39: 5161 3) ≥40: 721	≥ 24 wks	54.4% vs 29.7% vs 30.7%*	1.8% vs 4.7% vs 3.3%*	BMI (>24.2): 7.8% vs 7.8% vs 15.3%* Education (<9): 5.6% vs 6.9% vs 10.7%* Unmarried: 0.3% vs 0.1% vs 0.4% (NS)	Preexisting DM: 0.2% vs 0.4% vs 0.7%* Uterine fibroids: 0.5% vs 1.8% vs 3.1%* No history of induced abortion: 60.2% vs 47.9% vs 41.3%*	Gestational HTN/Pre-eclampsia: 1.7% vs 2.9% vs 4.9%* Gestational DM: 5.5% vs 11.6% vs 15.4%*
Jolly et al.	UK 2000	The risks associated with pregnancy in women aged 35 years or older	Retrospective population based cohort study (SMMIS database 18 Hospitals)	1) 18-34: 336462 2) 35-40: 41327 3) >40: 7331	Singleton pregnancies	46.2% vs 25.0% (NS) vs 20.5% (NS)	N/A	White: 72.9% vs 72.0% vs 69.4% (N/A) Asian: 13.9% vs 11.8% vs 12.6% (N/A) Black: 3.1% vs 2.9% vs 2.6% (N/A)	Chronic HTN: 4.7% vs 7.0% vs 8.9% (N/A) Preexisting DM: 0.4% vs 0.7% vs 1.0% (N/A)	Preeclampsia: 0.78% vs 0.76%* vs 0.79% (NS) (aOR 1.19[1.01, 1.40], aOR 1.25[0.88, 1.79]) Gestational DM: 1.0% vs 2.85%* vs 4.56%* (cOR 2.63[2.40, 2.89]), cOR 3.98 [3.38, 4.68])

Kullmer et al.	Germany 2000	Pregnancies in Primiparous women 35 or older: Still risk pregnancies?	Retrospective population based cohort (Hesse Perinatal Database)	1) 18-34: 154651 2) 35-39: 8883 3) >39: 1269	All primiparous births	100%	2.5% vs 6.6% (NS) vs 8.0%* (infertility treatment)	Homemaker: 11.0% vs 8.6%* vs 9.5% (NS) Smoking; 13.4% vs 10.6%* vs 9.1%* Obesity: 11.8% vs 9.8%* vs 9.1%*	Preexisting DM: 0.3% vs 0.5%* vs 1.1%* Coagulation disorders: 0.7% vs 1.2%* vs 1.8%* History of severe disease (unspecified): 5.2% vs 7.4%* vs 8.0%*	Transient HTN: 3.1% vs 3.4% (NS) vs 3.4% (NS) (cOR1,10[0.98, 1.26], cOR1.08[0.79,1.47]) Preeclampsia/Eclampsia: 4.0% vs 4.6%* vs 5.4%* (cOR1.16[1.05, 1.28], cOR1.35[1.06,1.73]) Gestational DM: 0.4% vs 0.7%* vs 1.3%* (cOR1.67[1.30, 2.15], cOR2.94[1.83, 4.73])
Tabcharoen et al.	Thailand 2009	Pregnancy outcome after age 40 and risk of low birth weight	Retrospective cohort study (Single center)	1) 20-34: 20852 2) ≥ 40: 789	≥ 28 wks	49.4% vs 20.8%*	N/A	Occupation* Government employee: 14.7% vs 31.3% Trained worker 40.8% vs 25.7% Housewife: 24.4% vs 20.9%	Chronic HTN: 0.1% vs 0.8%*	Pregnancy-induced HTN: 1.8% vs 3.7%*
									Preexisting and gestational diabetes: 0.6% vs 2.9%*	
Koo et al.	Taiwan 2012	Pregnancy outcomes according to increasing maternal age	Retrospective cohort study (1 hospital)	1) 20-29: 7950 2) 30-34: 15496 3) 35-39: 5665 4) ≥ 40: 649	≥ 14 wks	81.1% vs 56.7% vs 41.4% vs 40.5%*	1.2% vs 3.1% vs 5.9% vs 6.6%* (IVF)	BMI(kg/m2): 21.4 vs 21.7 vs 22.3 vs 23*	Chronic HTN: 0.3% vs 0.5% vs 0.8% vs 1.7%* Preexisting DM: 0.3% vs 0.5% vs 1.0% vs 0.9%* Prior pontaneous abortion: 12.4% vs 20.5% vs 28.7% vs 40.5%* Preexisting conditions: 2.8% vs 4.3% vs 5.9% vs 6.6%* (Preexisting conditions include chronic HTN,pregestational DM, cardiac disease, thyroid disease, epilepsy, and asthma)	Hypertensive complications: 2.1% vs 1.9% (NS) vs 2.3% (NS) vs 4.8%* (aOR1.0[0.8,1.2], aOR1.3[1.0,1.7], aOR2.8[1.8,4.3]) (Includes gestational HTN, preeclampsia, eclampsia) Gestational DM: 1.2% vs 2.5%* vs 4.4%* vs 6.8%* (aOR2.0[1.6,2.6], aOR3.6[2.8, 4.8], aOR5.1[3.3, 7.8])
Carolan et al.	Australia 2011	Older Maternal Age and Intervention in Labor: A Population-Based Study Comparing Older and Younger First-Time	Retrospective population based cohort study (Victorian Perinatal Data Collection)	1) 25-29: 16920 2) 35-39: 7830 3) 1247	All births	100%	N/A	Married: 73.7% vs 73.1% vs 66.1% (N/A) Admission Private: 31.5% vs 59.0% vs 60.0% (N/A)	Preexisting hypertension: 0.9% vs 1.7% vs 2.2% (N/A) Preexisting diabetes: 0.5% vs 0.8% vs 0.7% (N/A)	Preeclampsia/ HELLP: 4.3% vs 5.2% vs 6.1% (N/A) Gestational DM: 4.4% vs 6.6% vs 7.7% (N/A)
Diejomaoh et al.	Kuwait 2006	The reproductive performance of women at 40 years and over	Retrospective cohort study (1 hospital)	1) 25-30: 160 2) ≥ 40: 168	Singleton Births	20.6% vs 2.5%	N/A	Kuwaits: 45% vs 61.9%*	Chronic HTN: 0% vs 6.5%* (OR23.438[1.369,401.42]) Medical disorders: 2.5% vs 19.1%* (OR9.176[3.164,26.615]) (Includes chronic DM, HTN, cardiac disease, asthma, thyroid disease, endocrine disease, renal disease, anemia, previous surgeries)	Transiet hypertension: 3.8% vs 18.5%* (OR5.8.08[2.35,14.35])
									Preexisting and gestational diabetes: 6.3% vs 17.3%* (OR3.129[1.47,6.66])	
Ludford et al.	South Australia 2012	Pregnancy outcomes for nulliparous women of advanced maternal age in South Australia, 1998-2008	Retrospective population based cohort study	1) 25-29: 26273 2) 35-39: 7116 2) ≥40: 1306	≥ 20 wks	100%	N/A	Married: 91.6% vs 93.0%* vs 89.4%* White: 92.8% vs 93.9% vs 93.1% (NA) Asian: 6.5% vs 5.6%* vs 6.6% (NS) Private: 35.0% vs 55.4%* vs 58.7%* Country-side: 26.8% vs 17.3%* vs 16.7%* Smoking; 18.9% vs 15.6%* vs 15.2%*	Chronic HTN: 1.2% vs 2.5%* vs 3.7%* Preexisting DM: 0.4% vs 0.6% (NS) vs 0.7% (NS) Epilepsy: 0.5% vs 0.6% (NS) vs 0.4% (NS) Anemia: 4.7% vs 4.6% (NS) vs 5.6% (NS) Asthma:6.6% vs 5.3%* vs 5.7% (NS) Urinary tract infection: 2.4% vs 1.3%* vs 1.9% (NS)	Transient HTN: 11.0% vs 11.6% (NS) vs 11.7% (NS) (RR1.05 [0.98, 1.13], RR1.06[0.91,1.24]) Gestational DM: 3.3% vs 6.5%* vs 8.3%* (RR1.97 [1.77, 2.20], RR2.53[2.09, 3.07])

Seoud et al.	Lebanon 2002	Impact of advanced maternal age on pregnancy outcome	Retrospective matched cohort (Single center)	1) 20-30: 51 2) ≥ 40: 53	> 24 wks Singleton	100%	2.1% vs 9.4%	N/A	Chronic HTN: 2.0% vs 1.9% (NS)	Preeclampsia: 5.9% vs 5.7% (NS) Gestational DM: 0% vs 3.8% (NS)
				1) 20-30: 275 2) ≥ 40: 266		0%			Chronic HTN: 0.7% vs 5.3%*	Preeclampsia: 0% vs 4.1%* Gestational DM: 1.1% vs 5.6%*
Jahromi et al.	Iran 2008	Pregnancy outcome at maternal age 40 and older	Case control study (2 hospitals)	1) 20-30: 200 2) ≥ 40: 200	≥ 20 wks	62.5% vs 14%	N/A	N/A	Chronic HTN: 1% vs 3% (OR 3.06[0.61, 15.35])	Preeclampsia: 4.5% vs 18% (OR4.39[2.05-9.37])* Diabetic complications: 2% vs 5.5% (OR2.85[0.89,9.11])
Canto et al.	Spain 2012	Pregnancy outcome in a Spanish population of women beyond age 40 delivered above 32 weeks' gestation	Prospective cohort study (1 hospital)	1) 20-29: 347 2) ≥ 40: 335	≥ 32 wks	61.7% vs 23.9%*	N/A	N/A	Infertility: 1.2% vs 9.6%* Uterine fibroids: 0.3% vs 2.7%* Hypothyroidism: 1.7% vs 2.4% (NS)	Gestational DM: 2.3% vs 16.4%* Preeclampsia: 2.6% vs 6.8%*
Bianco et al.	US 1996	Pregnancy outcome at age 40 and older	Retrospective cohort study (Single center)	1) 20-29: 4635 2) ≥ 40: 607	Singleton pregnancies	100%	0.3% vs 8.7%* (history of IVF use)	White: 68.5% vs 87.9%* Married 90.8% vs 85.8% College education: 65.2% vs 84.3%* Tobacco use: 4.4% vs 3.5%	Chronic HTN: 0.5% vs 0.9% (NS) Preexisting DM: 0.3% vs 0.5% Cardiac disease: 2.2% vs 3.9%* Thyroid disease: 1.5% vs 2.6%* Renal disease: 0.7% vs 0.7% (NS) Asthma: 3.3% vs 3.3% (NS) Leiomyomas: 1.1% vs 10.1%*	Preeclampsia: 4.4% vs 7.4%* (aOR 1.8[1.3, 2.6]) Gestational DM: 4.3% vs 10.5%* (aOR 2.7 [1.9, 3.7])
						66.4% vs 43.2%				
				1) 20-29: 2343 2) ≥ 40: 797		0%	0.2% vs 2.3%* (history of IVF use)	White: 65.7% vs 83.4%* Married 92.7% vs 94.8% College education: 41.1% vs 77.1%* Tobacco use: 2.5% vs 1.5%	Chronic HTN: 0.6% vs 2.1%* Preexisting DM: 0.5% vs 0.8% (NS) Cardiac disease: 1.9% vs 4.1%* Thyroid disease: 1.5% vs 3.4%* Renal disease: 0.6% vs 0.5% (NS) Asthma: 3.3% vs 3.5% (NS) Leiomyomas: 1.1% vs 4.6%*	Preeclampsia: 2.7% vs 5.3%* (aOR 1.9 [1.2, 2.9]) Gestational DM: 2.9% vs 10.8%* (aOR 3.8 [2.7, 5.4])
Gilbert et al.	US 1999	Childbearing Beyond Age 40: Pregnancy Outcome in 24,032 Cases	Retrospective population based cohort study (database from California Office of Statewide Health Planning)	1) 20-29: 258900 2) ≥ 40: 4777	All births	100%	N/A	White: 39% vs 64%* Hispanic: 43% vs 14%* Asian: 11% vs 17%* Black: 6% vs 4%	Chronic HTN: 0.3% vs 1.6%*	Preeclampsia: 3.4% vs 5.4% * (aOR 1.8 [1.6, 2.1]) Gestational DM: 0.5% vs 1.4%* (aOR 3.3[2.5, 4.2]) Abnormal glucose tolerance: 1.7% vs 7.0%* (aOR4.0 [3.6, 4.5])
				1) 20-29: 383625 2) ≥ 40: 19255		0%		White: 31% vs 41%* Hispanic: 52% vs 36%* Asian: 7% vs 18%* Black: 9% vs 5%*	Chronic HTN: 0.2% vs 1.8%*	Preeclampsia: 1.0% vs 2.7% * (aOR 3.1[2.8,3.4]) Gestational DM: 0.5% vs 2.7%* (aOR 6.4[5.8, 7.1]) Abnormal glucose tolerance: 1.6% vs 7.8%* (aOR 4.0 [3.6,4.5])
Joseph et al.	Canada 2005	Perinatal effects of delayed chilbearing	Retrospective population based cohort study (Nova Scotia Atlee Perinatal Database)	1) 20-24: 35711 2) 25-29: 53647 3) 30-34: 40068 4) 35-39: 13551 5) ≥ 40: 1822	Singleton Births	57.5% vs 43.0% vs 29.8% vs 23.4% vs 21.2%	N/A	Married: 43.6% vs 78.2% vs 85.0% vs 83.2% vs 79.5% Smokers: 29.4% vs 31.5% vs 30.7% vs 31.0% vs 32.7% Weight (≥70kg): 29.4% vs 31.5% vs 30.7% vs 31.0% vs 32.7% High income: 2.5% vs 11.6% vs 20.9% vs 26.0% vs 23.2%	Chronic disease: 2.65% vs 3.56%* vs 4.31%* vs 5.40%* vs 5.98%* Chronic HTN, transient HTN, HELLP, eclampsia: 1.98% vs 2.30%* vs 2.56%* vs 3.25%* vs 5.21%* Pre-existing and gestational DM: 0.26% vs 0.36%* vs 0.51%* vs 0.49%*	

ART: Artificial reproductive technology
HTN: Hypertension
DM: Diabetes Mellitus

OR: Odds ratio
aOR: Adjusted odds ratio
N/A: Not available

NS: Not significant compared to reference group
* Significant difference compared to reference group
Reference age groups are the youngest age group for each study

Table 3. Studies using 45 years of age as the cut-off value for the advanced maternal age group (n=6)

Author	Count Year	Title	Study design	Age Groups: Sample Size	Enrollment Criteria	Nulliparous	ART	Characteristics	Pre-existing Conditions	Outcomes
Dulitzki et al.	Israel 1998	Effect of very advanced maternal age on pregnancy outcome and rate of cesarean delivery	Retrospective cohort study (1 hospital)	1) 20-29: 309 2) ≥44: 109	Singleton births	42.1% vs 32.1%	6.5% vs 26.6%*	N/A	Pregestational disease: 7.3% vs 15.6%* (thyroid dysfunction, asthma, Crohn's disease, cardiac disease, hematologic disorders, epilepsy, diabetes mellitus, hypertension, or ITP)	Hypertensive Disorders: 4.9% vs 12.8% (NS) Gestational DM: 4.2% vs 4.6% (NS)
Abu-Heija et al.	Jordan 2000	Maternal and perinatal outcome of pregnancies after the age of 45	Retrospective cohort study (1 hospital)	1) 20-29: 121 2) ≥45: 114	> 28 wks	1.8 vs 7.6* (in parity)	N/A	N/A	Chronic HTN: 0.8% vs 4.4% (NS) Chronic DM: 0.8% vs 9.6%* Cardiac disease: 0% vs 0.9% (NS)	Diabetic complications: 0.8% vs 9.6%* Preeclampsia: 1.6% vs 12.3%*
Jacobsson et al.	Sweden 2004	Advanced maternal age and adverse perinatal outcome	Retrospective population based cohort study (Swedish Birth Registry)	1) 20-29: 876361 2) 40-44: 31662 3) ≥45: 1205	All births	51.0% vs 17.1%* vs 15.2%*	N/A	Married/cohabiting: 95.1% vs 89.6%* Smoking 20.8% vs 15.6%* Homogenous white race, high education, low alcohol and drug use, adequate prenatal and obstetrics care	Hypertensive disease: 0.23% vs 0.93%* vs 1.41%* Preexisting DM: 0.36% vs 0.57% vs 0.33% (NS) Renal disease: 0.36% vs 0.57% vs 0.50% (NS) Disseminated lupus erythematosus: 0.06% vs 0.12 vs 0.25* Bronchial asthma: 3.10% vs 2.87% vs 3.32% (NS) Ulcerative colitis: 0.26% vs 0.37% vs 0.75*	Transient hypertension: 0.55% vs 1.78%* vs 3.40%* Mild preeclampsia: 2.11% vs 1.24%* vs 0.66%* Severe preeclampsia: 0.81% vs 1.12%* vs 1.49%* Gestational DM: 0.28% vs 0.97%* vs 1.33%*
Yogev et al.	Israel 2010	Pregnancy outcome at extremely advanced maternal age	Prospective cohort study (1 hospital)	1) 20-29: 1770 2) 30-39: 1770 2) 40-44: 1770 4) ≥45: 177	≥ 24 wks	72.7% vs 53.9% vs 33.1% vs 39%*	N/A	N/A	Obesity(BMI≥30): 19% vs 20% vs 23% vs 24% Chronic HTN: 0.1% vs 0.8% vs 2.7% vs 6.8%* Preexisting DM: 0.8% vs 1.1% vs 1.4% vs 4.5%*	Gestational HTN: 2.0% vs 2.3% vs 3.2% vs 9.0%* Preeclampsia: 0.7% vs 1.5% vs 2.4% vs 10.7%* Gestational DM: 1.4% vs 4.2% vs 10.2% vs 17.0%*
Laskov et al.	Israel 2012	Outcome of singleton pregnancy in women	Retrospective cohort study (1 hospital)	1) <40: 304 2) ≥45: 278	≥ 20 wks Singletons	54% vs 46%	100% (IVF)	N/A	Preexisting DM: 0% vs 0.7% Preexisting HTN: 0.36% vs 6.1%* Thyroid disorders: 4.9% vs 6.8% Leiomyomas: 1.5% vs 10.4%*	Gestational HTN: 2.3% vs 8.3%* Severe Preeclampsia: 1.0% vs 7.9%* Gestational DM: 10.2% vs. 21.2%*
Luke and Brown	US 2007	Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age	Retrospective population based cohort study (US National Center for Health Statistics)	1) 30-34: 1480165 (ref) 2) 35-39: 532784 3) 40-44: 94026 4) ≥ 45: 3979 1) 30-34: 3731682 (ref) 2) 35-39: 1867144 3) 40-44: 355860 4) ≥ 45: 14356	Liveborn Singletons	100% 0%	N/A	White: 82.8% vs 82.0% vs 80.4% vs 78.9% Black: 10.4% vs 11.0% vs 11.8% vs 10.7% (N/A) Education (<12): 9.9% vs 9.9% vs 12.1% vs 17.9%* Smoker: 7.1% vs 7.8% vs 7.1% vs 5.0%*	Chronic HTN: 1% vs 1.6%* vs 2.6%* vs 3.4%* Preexisting or Gestational DM: 3.5% vs 4.8%* vs 6.1%* vs 7.2%* Chronic HTN: 0.8% vs 1.3%* vs 2.3%* vs 3.6%* Preexisting or Gestational DM: 3.4% vs 4.7%* vs 6.4%* vs 8.6%*	Pregnancy-associated HTN: 5.0% vs 5.6%* vs 6.2%* vs 7.4%* Pregnancy-associated HTN: 2.4% vs 2.9%* vs 3.7%* vs 4.7%*

ART: Artificial reproductive technology
HTN: Hypertension
DM: Diabetes Mellitus
ITP: Idiopathic thrombocytopenic purpura

OR: Odds ratio
aOR: Adjusted odds ratio
N/A: Not available

NS: Not significant compared to reference group
* Significant difference compared to reference group
Reference age groups are the youngest age group for each study

Table 4. Studies using 50 years of age as the cut-off value for the advanced maternal age group (n=5)

Author	Count Year	Title	Study design	Age Groups: Sample Size	Enrollment Criteria	Nulliparous	ART	Characteristics	Pre-existing Conditions	Outcomes
Glasser et al.	Israel 2011	Primiparity at very advaced maternal age (≥45 years)	Retrospective cohort study (Single center)	1) 45-49: 105 2) 50-65: 26	All births	100%	N/A vs 100% (IVF)	Married/stable partner: 47.6% vs 61.5%	Chronic condition: 30.3% vs 34.6% (thyroid, HTN, DM, hematologic, cardiac disorders) Chronic HTN: 6.1% Preexisting DM: 2.3%	Gestational DM: 42.9% vs 42.3% (NS) Gestational HTN: 36.3% vs 68.2% (NS) Preeclampsia: 17.1% vs 23.1% (NS)
Chibber	Saudi Arabia 2005	Child-bearing beyond age 50: pregnancy outcome in 59 cases "a concern?"	Retrospective cohort study (1 hospital)	1) 20-29: 60 2) 50-55: 59	All births	100% 0%	0% vs 96.5% (IVF)	Arabs: 18% vs 20% Asians: 12% vs 8% Arabs: 19% vs 20% Asians: 11% vs 11%	No chronic conditions	Gestational DM: 1% vs 6%* (aOR4.0[2.5, 4.2]) Mild Preeclampsia: 7.1% vs 14.4%* (aOR3.8[1.6,2.1]) Severe preeclampsia: 3.3% vs 9.0%* (aOR4.4[1.2,2.4]) Gestaional DM: 4% vs 12.3%* (aOR3.5[3.6,4.5]) Miled preeclampsia: 1.2% vs 6%* (aOR3.1[2.9,3.4]) Severe preeclampsia: 0% vs 1.2%* (aOR2.7[1.8,3.6])
Simchen et al.	Israel 2006	Pregnancy outcome afte	Prospective cohort study (1 hospital)	1) 45-49: 99 2) ≥ 50: 24	All births	50% vs 71%	Egg donation: 13% vs 100%	N/A	Preexisting DM: 1% vs 8%*	Transient HTN: 27% vs 33% (NS) Severe HTN comp: 11% vs 4% (NS) Gestational DM: 19% vs 29% (NS)
Kort et al.	US 2012	Pregnancy after Age 50: Defining Risks for Mother and Child	Retrospective cohort study (Single center)	1) < 42: 41 2) ≥ 50: 101	> 23 wks	0.63 vs 0.79 (in parity, not in %)	N/A vs 100% (IVF)	N/A	Chronic HTN: 0% vs 4% Preexisting DM: 2.4% vs 1%	Transient HTN: 0% vs 6.9% (NS) Mild Preeclampsia: 2.9% vs 8.9% (NS) Severe preeclampsia: 11.4% vs 7.9% (NS) GDM-A1: 2.8% vs 2% (NS) GDM-A2: 0% vs 2.0% (NS)
Antinori et al.	Italy 2002	Obstetric and prenatal outcome in menopausal women: a 12-year clinical study	Prospective cohort study (1 hospital)	1) 45-50: 826 2) 51-60: 323	All pregnancies	86.80%	N/A vs 100% (IVF)	Pregnancy rate: 38.2% vs 37% Delivery rate: 9.7% vs 10.6% Multiple pregnancies: 6.7% vs 6.4%	No chronic conditions	Hypertensive disorders: 11.9% vs 11.7% (Includes transient HTN, Preeclampsia, and Eclampsia)

ART: Artificial reproductive technology
HTN: Hypertension
DM: Diabetes Mellitus
OR: Odds ratio
aOR: Adjusted odds ratio
N/A: Not available
NS: Not significant compared to reference group
* Significant difference compared to reference group
Reference age groups are the youngest age group for each study

Chapter 2. Thesis Manuscript

The Association between Advanced Maternal Age and Adverse Hypertensive and Diabetic Complications During Pregnancy:

A Six-year Retrospective Cohort Study in Metro Atlanta, USA

By

Momoko Kitami

OBJECTIVE: To investigate the effects of advanced maternal age on adverse hypertensive and diabetic complications of pregnancy, in relation to other major risk factors.
METHODS: A retrospective cohort study using Kaiser Permanente Georgia electronic health data of pregnant women receiving prenatal care in 12 Kaiser-affiliated Obstetrics and Gynaecology facilities between January 1, 2005 and August 31, 2011, with linked Georgia Birth Certificate data. Women were divided into two age groups: 1) reference group who were 35-39 years old, and 2) advanced maternal age (AMA) group who were 40 years and older. Adjusted risk ratios (aRR) were calculated after adjusting for correlation among women with multiple pregnancies, and relevant confounders (maternal race, obesity, infertility, gravidity, maternal education, marital status, and pre-existing medical conditions) using log-Binomial or log-Poisson regression analysis.
RESULTS: A total of 1181 pregnancies of 1096 women (939 women in reference group, 157 in AMA group) were included in the study. Risk of chronic hypertension was significantly higher in the AMA group (adjusted risk ratio [aRR], 2.05; 95%CI, 1.48-2.86), but risk of transient hypertension (aRR, 1.07; 95%CI, 0.51-2.22), mild preeclampsia (aRR 1.31; 95%CI, 0.61-2.81), severe preeclampsia/eclampsia (aRR 0.87; 95%CI, 0.26-2.86), chronic diabetes (aRR 0.74; 95%CI, 0.37-1.50), and gestational diabetes (aRR 0.97; 95%CI, 0.59-1.59) were not significantly increased in the AMA group. When risk of having any hypertensive complications was evaluated separately for white and black maternal race, AMA remained a significant risk factor among blacks (p=0.002), but note whites (p=0.15). Although risk of having preeclampsia or eclampsia was more fully explained by history of chronic hypertension and marital status than AMA, no significant risk factor was identified for transient hypertension. Obesity, primigravida, and Asian maternal race were identified as more significant risk factors for gestational diabetes compared to AMA.
CONCLUSION: Advanced maternal age is an important risk factor for chronic hypertension, but other risk factors such as obesity, maternal race, gravidity, and pre-existing medical conditions may play a larger role in the development of preeclampsia, eclampsia, and gestational diabetes. Strength of association of these risk factors may vary depending on maternal race.

I. Introduction

In many developed nations and some developing countries, postponement of parenthood is becoming an increasing trend due to rise in female employment and higher education, the growing availability of contraceptive pills, changes in cultural norms concerning marriage, and financial difficulties during young adulthood (1). In the United States, the proportion of women who are 35 years or older among all women giving birth to their first child, rose from one in 100 in 1970 to one in 12 in 2006 (2, 3). This trend in delaying childbearing has brought greater attention to the negative obstetrical consequences of conceiving at an advanced maternal age. Epidemiologic studies have shown that fecundability (probability of conceiving) and fertility (live birth rates) decreases with maternal age (4, 5), while risk of miscarriage increases significantly among mothers of ages 35 and older (6). Even after successful conception and pregnancy through term, advanced maternal age is known to be associated with various adverse pregnancy outcomes such as intrauterine growth restriction (7, 8), cesarean delivery (9, 10, 11), and congenital anomalies (e.g. Down syndrome, Trisomy 21), and possibly prenatal mortality and stillbirth (12, 13, 14) compared to younger mothers between ages 20 and 29 (4, 15).

Among various pregnancy complications, hypertensive and diabetic complications have been a major topic of research due its potentially life-threatening effects on both the fetus and the mother. Hypertensive disorders alone are the second leading cause of maternal death in developed countries, accounting for 16.1% of total maternal deaths (16, 17). They are the leading cause of maternal morbidity in Latin America and the Caribbean, accounting for 25.7% of maternal deaths (17). Poor management of hypertension, preeclampsia and eclampsia is one of the major causes of maternal mortality and stillbirth developing countries (18, 19).

The growing prevalence of obesity, hypertension, and diabetes around the globe are also of concern, as women with chronic hypertension are at higher risk for developing severe forms of hypertensive complications such as preeclampsia and eclampsia. Studies show that 20 to 25% of

women with chronic hypertension develop preeclampsia, and chronic hypertension alone increases the risk for preterm birth, low birth weight infants, and small for gestational age infants (20, 21). In the US, the overall maternal morbidity has remained the same in the last several decades, but the incidence of transient (gestational) hypertension and preeclampsia have been increasing due to increase in prevalence of known risk factors such as chronic hypertension, pre-gestational diabetes, and obesity (22, 23). Management of hypertensive patients is essential in obstetrics care, since the development of preeclampsia can lead to major complications for the infant, such as respiratory distress syndrome and intrauterine growth restriction (24). Screening and management of patients with diabetic disorders are also important part of routine obstetrics care, as diabetic complications increase the risk of post-partum haemorrhage, infections, and prolonged labor for the mother, and increase the risk of spontaneous abortion, stillbirth, macrosomia, shoulder dystocia, malformation, neonatal hypoglycaemia, and infant respiratory distress syndrome for the newborn (25, 26). Even after childbirth, having diabetic complications during pregnancy has known to increase the risk of developing type-2 diabetes and cardiovascular diseases in the future (16, 25, 26).

In order to better screen high-risk patients and prevent them from life-threatening outcomes, researches have tried to identify risk factors and pre-existing conditions that may be strongly associated with the development of hypertensive and diabetic complications. Risk factors such as obesity, nulliparity, multiple gestations, history of preeclampsia in previous pregnancies, family history of preeclampsia, change of paternal gametes between pregnancies, and use of donor gametes have been known to be associated with preeclampsia (27-30), and pre-existing medical conditions such as chronic hypertension, pre-gestational diabetes, renal diseases, vascular and connective tissue diseases, autoimmune diseases, and antiphospholipid antibody syndrome have also been found to be associated with preeclampsia (16). Risk factors that have been identified for gestational diabetes are obesity, previous history of gestational diabetes,

family history of type-2 diabetes, ethnicity, history of polycystic ovary syndrome (PCOS), and maternal age (33).

Although results are not conclusive, some studies suggest that hypertensive complications of pregnancy may be a part of a spectrum of insulin resistance syndrome, as many risk factors for hypertensive and diabetic pregnancy complications are shared, and metabolic disorders that alter insulin resistance such as gestational diabetes, PCOS, and excessive weight gain during pregnancy are known to be associated with hypertensive pregnancy complications such as transient hypertension and preeclampsia (34-36). Studies have also shown that patients with chronic hypertension may have a greater risk of gestational diabetes (37), and patients with hypertensive complications during pregnancy are more likely to have gestational diabetes compared to normotensive women (38).

The interconnectedness of risk factors makes it difficult for clinicians to understand how important the relative contributions of various risk factors are, and what role maternal age plays in increasing these risks since prevalence of chronic hypertension and diabetes increases with obesity and maternal age (39). Whether maternal age itself or the underlying increase in other risk factors, such as obesity and gravidity, explains the observed increases in pregnancy complications remains unclear. It is vital for health practitioners to understand how risk factors for hypertensive and diabetic complications change as mothers postpone childbearing, when there are combinations risk factors. Few studies have focused on the relative importance of advanced maternal age as a risk factor compared to other risk factors of hypertensive and diabetic complications. In part, this is due to the lack information on pre-existing medical conditions, obesity, gravidity, and infertility of the study population in previous studies. There is also great inconsistency and ambiguity in previous studies with regards to their definition of outcomes, which makes interpretation of evidence across studies a challenging process.

Therefore, the purpose of this study is to investigate the effects of advanced maternal age in relation to other major risk factors of hypertensive and diabetic complications of pregnancy. In

particular, this study will focus on transient hypertension, preeclampsia/eclampsia, and gestational diabetes as outcomes of interest, and study the effects of advanced maternal age in relation to other risk factors such as history of hypertensive and diabetic disorders, obesity, gravidity, and race.

II. Methods

We conducted a retrospective cohort study using electronic medical records with linked Georgia Birth Certificate (BC) data to investigate the association between advanced maternal age (40 years old and over: AMA ≥40) and adverse hypertensive and diabetic pregnancy complications among a cohort of women over 35 years of age and older at time of their first prenatal visit. We also compared AMA with other potential risk factors of hypertensive and diabetic complications to explore whether AMA plays a larger role in the development of these pregnancy complications compared to other risk factors.

Hypotheses and objectives

The main purpose of this study is to examine the effects of AMA (≥40 years old) on hypertensive and diabetic complications of pregnancy. Two primary research questions will be addressed:

Aim 1)

The first aim is to examine whether there is an increased risk for the following hypertensive and diabetic complications among pregnant women of ages 40 and above, compared to women between ages 35 to 39 at the time of their first prenatal visit. The effect of AMA on the following outcomes will be studied.

Hypertensive complications during pregnancy

1. Any hypertensive complications (chronic hypertension, transient hypertension, preeclampsia, and eclampsia)
2. Chronic hypertension

3. Transient hypertension
4. Preeclampsia / Eclampsia (includes mild preeclampsia, severe preeclampsia, and eclampsia)

Diabetic complications during pregnancy

1. Any diabetic complications (chronic diabetes mellitus and gestational diabetes)
2. Chronic diabetes
3. Gestational diabetes

The null hypothesis is that there is no difference in the risk of developing each of the five hypertensive and diabetic complications in the AMA group compared to younger mothers.

Aim 2)

The second aim is to investigate the effects of AMA on adverse hypertensive and diabetic complications in relation to other risk factors such as obesity, gravidity, infertility, maternal race, marital status, maternal education, history of diabetic and hypertensive complications. The null hypothesize is that the effects of AMA on the risk of hypertensive and diabetic complications are smaller than other potential risk.

Data collection

We used Kaiser Permanente Georgia (KPGA) electronic health data of pregnant women receiving prenatal care in 12 Kaiser-affiliated Obstetrics and Gynaecology (OB/GYN) facilities: West Cobb Medical Center, Snellville Medical Office, Crescent Medical Center, Panola Medical Center, Glenlake Medical Center, Southwood Medical Center, TownPark Medical Center, Cumberland Medical Center, Cascade Medical Center, Gwinnett Medical Center, Eastside Medical Center, and Alpharetta Medical Center.

Pregnancy was defined as woman with a record of their first prenatal (FOB) visit and a pregnancy or delivery-related diagnosis or procedure within 9 months of the FOB (Table 2). All KPGA Health Plan members who 1) were enrolled at any time (i.e., at least one day) between

January 1, 2005 and November 2012, 2) had an FOB visit between January 1, 2005 and August 31, 2011 during or before their 12th week of pregnancy, and 3) were at least 35 years old at the time of their visit were enrolled in the study. Women with singleton and multiple pregnancies, as well as nulliparous and multiparous women were included in the study.

Women with dates for their FOB visits, but without a pregnancy or delivery-related diagnosis or procedure within 9 months of the FOB were excluded from the study. Women must be continuously enrolled in KPGA Health Plan from the date of the FOB through 10 months following the FOB to be included in the study. Gaps in enrollment of up to 45 days each, and multiple gaps in enrollment of KPGA Health Plan were permitted as long as no single gap was more than 45 days.

Pregnancy start date was calculated as 280 days before the expected date of delivery (EDD). EDD was recorded at the FOB visit, and if there were multiple EDDs record in the electronic medical records for a given FOB visit, the most recent EDD between FOB visit date and subsequent 60 days was used. If a woman did not have an EDD, but had a last menstrual period (LMP) date, LMP recorded at the FOB was used to determine whether she fulfilled the 12th week of pregnancy eligibility criterion. If neither EDD nor LMP were available for the pregnancy of interest, the woman was excluded from the study.

Data of 2201 FOB visits was extracted. From this dataset, a total of 34 FOB visits were deleted during the data cleaning process. This included 17 FOB visits that had no information on the outcome of the pregnancy, and 17 FOB visits where the outcome of a following pregnancy was linked to a previous FOB date. After any potential discrepancies were checked, the final cohort consisted of 2167 FOB visits from 1977 women. BC data was linked to maternal data for women whose BC data was available through Georgia Department of Community Health. This subset consisted of 1181 FOB visits from 1102 pregnant women. Data extracted from BC data used in this study include parity, gravidity, maternal education, marital status, pre-existing hypertension, gestational hypertension, gestational diabetes and pre-pregnancy diabetes. Dataset

with linked BC data (1181 FOB visits of 1102 pregnant women) was compared against the dataset without linked BC data (1977 women and 2167 FOB visits), to assess whether there were significant differences in the two datasets with regards to patient demographics, history of medical conditions, and pregnancy outcomes. For women with multiple FOB visits, the earliest FOB visit between January 1, 2005 and August 31, 2011 was used to create a table for patient characteristics, but data from all pregnancies were used for the analysis. Therefore, the final dataset consisted of 2167 FOB visits of 1977 women, but a subset data of 1181 FOB visits of 1102 pregnant with linked BC data was used primarily in the analysis.

Women were categorized into two age groups according to their age at their FOB visits. The dataset without linked Georgia BC data had 431 FOB visits of 371 women who were 40 or older, and 1736 FOB visits of 1606 women who were between 35 and 39 at the time of their FOB visit. The subset of this dataset with linked BC data consisted of 1003 FOB visits of 943 women in the AMA group, and 178 FOB visits of 159 women in the younger group.

One KPGA programmer pulled pre-existing medical conditions and disease outcomes from KPGA's electronic medical records using ICD-9-CM codes. All diagnoses made prior to FOB date were recorded as history or pre-existing conditions. Diagnoses recorded at FOB or within10 months following FOB date were recorded as having occurred during pregnancy except for pre-existing or chronic hypertension diagnosis given during pregnancy (ICD-9-CM 642.2 or 401-405).

Demographic information consisted of maternal age at FOB, gestational age of the fetus at FOB, maternal pre-pregnancy body mass index (BMI, kg/m^2), obesity ($BMI \geq 30$), and maternal race. Information regarding parity, gravidity, maternal education, and marital status were extracted through linked BC data. Maternal pre-pregnancy BMI was calculated using the most recent weight and height measurements recorded up to one year before the FOB, or recorded at the FOB visit. Calculated pre-pregnancy BMI was used to categorize women as obese if their BMI was 30 kg/m^2 or greater, and not obese if they had a BMI of less than 30 kg/m^2. Maternal

race was categorized into four groups: 1) Black/African American, 2) White, 3) Asian, and 4) Other, which consisted of Native Hawaiian, Other Pacific Islander, American Indian/Alaska Native, multiracial, unknown, or unreported. Maternal education was also categorized into four groups: 1) less than 8th grade education or completed some high school (without diploma), 2) high school graduate, obtained GED (General Educational Development), or some college-level education, 3) completed associate's or bachelor' degree, and 4) completed a masters degree or doctorate degree.

Pre-existing medical conditions extracted from KPGA electronic medical records using ICD-9-CM codes included transient hypertension (ICD-9-CM 642.3), mild preeclampsia (ICD-9-CM 642.4), severe preeclampsia (ICD-9-CM 642.5), eclampsia (ICD-9-CM 642.6), chronic hypertension (ICD-9-CM 642.2, 401-405), gestational diabetes (ICD-9-CM 648.8), Diabetes mellitus complicating pregnancy childbirth or the puerperium (ICD-9-CM 648.0), abnormal glucose tolerance test unrelated to pregnancy (ICD-9-CM 790.2), chronic diabetes (ICD-9-CM 249-250), thyroid disorder complications during previous pregnancy (ICD-9-CM 648.1), depression (ICD-9-CM 296.2-296.36, 311), seizure disorders (ICD-9-CM 345), thyroid disorders (ICD-9-CM 240-246), autoimmune disorders (ICD-9-CM 555, 556, 710.0, 714), hypercoagulative disorders (ICD-9-CM 289.81, 289.82), deep vein thrombosis (ICD-9-CM 453.2-453.9), pulmonary embolism (415.1), anemia in previous pregnancies (ICD-9-CM 648.2), infertility (includes ovarian dysfunction (ICD-9-CM 256), menopause (ICD-9-CM 627), or use of infertility-related drugs listed on Table 3), bacterial vaginosis (ICD-9-CM 616.1), candidiasis (ICD-9-CM 112.1), and urinary tract infection (ICD-9-CM 599.0).

a. Hypertensive complications

For study outcomes, the following adverse pregnancy complications were studied: transient hypertension, mild preeclampsia, severe preeclampsia, eclampsia, and gestational diabetes. Hypertensive diagnoses were made from a combination of seven diagnosis codes from

KPGA electronic medical records (hypertension code from ICD-9-CM 401-405, pre-existing hypertension code from ICD-9-CM 642.2, transient hypertension code from ICD-9-CM 642.3, preeclampsia/eclampsia superimposed on chronic hypertension code from ICD-9-CM 642.7, mild preeclampsia code from ICD-9-CM 642.4, severe preeclampsia code from ICD-9-CM 642.5, and eclampsia code from ICD-9-CM 642.6). First, diagnoses codes from KPGA electronic medical records were used to categorize patients into various hypertensive outcomes.

Transient hypertension was defined as hypertension developing after 20 weeks of gestation, but resolving within 12 weeks, postpartum. If hypertension (blood pressure ≥ 140/90mmHg confirmed on two separate occasions) was present before 20 weeks of gestation or persisted more than 12 weeks postpartum, the patient was diagnosed as having chronic hypertension. De novo hypertension beyond 20 weeks gestation with significant proteinuria was diagnosed as mild preeclampsia. Severe preeclampsia was diagnosed if resting blood pressure of over 160mmHg systolic or 110mmHg diastolic blood pressure was observed on two separate occasions, or if proteinuria or signs for organ injury were observed. Eclampsia was diagnosed when seizures developed in addition to preeclampsia, but may develop rapidly without signs of preeclampsia.

Diagnosis codes for hypertensive complications were cleaned in the following manner. Patients who had an ICD-9-CM code for chronic hypertension (ICD-9-CM 401-405) from KPGA data within the first 20 gestational weeks were left as having chronic hypertension (5 observations). However, mothers with chronic hypertension ICD-9-CM code entered after 20 gestational weeks were categorized as transient hypertension, but not chronic hypertension (35 observations). Patients, who were diagnosed with transient hypertension within the first 20 gestational weeks, were re-coded as having had chronic hypertension, and not transient hypertension (4 observations). Therefore, if a patient had diagnosis codes for both chronic and transient hypertension, they were marked as chronic hypertension either of the two diagnosis dates was before 20 gestational weeks (12 observations). If dates of diagnosis for both chronic

and transient hypertension were beyond 20 gestational weeks, the patient was marked as having transient hypertension, but not chronic hypertension (1 observation).

Additionally, patients were marked as having or not having mild preeclampsia or severe preeclampsia/eclampsia. Patients who had transient hypertension and subsequently developed preeclampsia or severe preeclampsia were counted as having the more severe category (preeclampsia or eclampsia), and were excluded from the moderate category (transient hypertension).

After data for hypertensive outcomes were cleaned using the above method, they were compared against data from BC data to observe whether there were any inconsistencies in diagnosis codes between KPGA data and BC data. Three codes for hypertensive complications from linked Georgia BC data (pre-pregnancy hypertension, gestational hypertension, and eclampsia) were compared against KPGA diagnoses. There were 13 observations coded as transient hypertension by BC data, but as chronic hypertension according to KPGA data. There were 16 observations coded as transient hypertension by BC data, but had preeclampsia or eclampsia according to KPGA data. Overall, KPGA was completely inclusive of BC data, and 323 observations did not have any hypertensive diagnostic codes according to BC data, but had some type of hypertensive diagnostic codes according to KPGA data. Therefore, the three BC diagnostic codes (pre-pregnancy hypertension, gestational hypertension, and eclampsia) were not used.

b. Diabetic complications

Diabetes-related diagnoses were made by a combination of four diagnosis codes from KPGA electronic medical records (diabetes diagnosis code from ICD-9-CM 249-250, abnormal glucose tolerance test code from ICD-9-CM 790.2, gestational diabetes code from ICD-9-CM 648.8, diabetes mellitus complicating pregnancy childbirth or the puerperium code from ICD-9-CM 648.0). There were three codes for diabetic complications from linked BC data (diabetes,

pre-pregnancy diabetes, and gestational diabetes). Screening for gestational diabetes was performed by giving 50-gram oral glucose 1-hr loading test on FOB visit for women who are at risk of gestational diabetes, and to all members between 24 to 26 gestational weeks regardless of their risk. Women were defined as being at risk for gestational diabetes if they had any of the following risk factors: 1) history of gestational diabetes in previous pregnancies, 2) history of birth to a baby weighing more than 9lbs, 3) obese and young (age ≤ 25 years old), or 4) age 35 and older. Further diagnosis of gestational diabetes was done by 100-gram oral glucose 3-hour tolerance test. The American Congress of Obstetricians and Gynecologists (2011) recommendations using Carpenter and Coustan serum glucose levels were used for diagnosing gestational diabetes (2 or more thresholds exceeded from fasting serum glucose level 95 mg/dL, 1-hr serum glucose level 180mg/dL, 2hr level 155 mg/dL, or 3hr 140mg/dL).

Patients were diagnosed as chronic diabetes if they had either ICD-9-CM codes for diabetes mellitus (ICD-9-CM 249-250) or Diabetes mellitus complicating pregnancy childbirth or the puerperium (ICD-9-CM 648.0). Patients diagnosed with diabetes (ICD-9-CM 249-250) prior to FOB date, but were diagnosed as having gestational diabetes during pregnancy (ICD-9-CM 648.8) were included in the chronic diabetes category and excluded from gestational diabetes category. If a patient had an ICD-9-CM code for abnormal glucose tolerance test during pregnancy (ICD-9-CM 790.2), they were categorized as having gestational diabetes.

KPGA diagnoses were compared against BC data to investigate whether there were any inconsistencies in diagnosis codes between KPGA data and BC data. There were 5 observations that had chronic diabetes according to BC data but no history of diabetes in KPGA data, and 3 observations that had gestational diabetes according to BC data but not diagnosed with gestational diabetes according to KPGA data. There were 113 observations diagnosed with chronic diabetes according to KPGA data, but not in BC data, and 148 observations diagnosed with gestational diabetes according to KPGA data, but not in BC data. There were a total of 25 observations with inconsistent outcomes: 10 observations diagnosed with chronic diabetes

according to KPGA data, but diagnosed as gestational diabetes according to BC data, and 15 observations diagnosed with gestational diabetes according to KPGA, but diagnosed as chronic diabetes according to BC data. Because KPGA was more inclusive compared to BC data, diagnosis outcomes from KPGA data was used.

Preterm birth was diagnosed using information on gestational weeks from BC data, and was therefore only determined for pregnancies with linked BC data. Preterm birth was defined as births occurring prior to completion of 37 gestational weeks. Caesarean section (654.02-654.23, procedure code 74), spontaneous abortion (ICD-9-CM 634), induced abortion (ICD-9-CM 635), and other types of abortions including illegal abortion and unspecified abortion (ICD-9-CM 636, 637), were obtained from KPGA medical records. Abnormal pregnancy was defined as ectopic pregnancies, molar pregnancies, and other abnormal conceptions not resulting in birth (ICD-9-CM 630, 631, 632, 633).

The protocol of this study was approved by the Institutional Review Boards of the corresponding institutions: Kaiser Permanente, Piedmont Medical Center, Northside Medical Center, and Emory University. None of the women were contacted or recruited for participation. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC). All statistical tests were two-tailed, with significance level at 0.05.

Data analysis

First, descriptive statistics for all mothers in the cohort were evaluated for continuous variables including maternal age at FOB visit (years), body mass index (BMI, kg/m2), and gestational age at FOB (weeks) using pooled two sample t-tests for evaluating mean differences between young age group and AMA group. For categorical variables maternal race and obesity, differences in proportion were evaluated using χ^2 test. Additional descriptive analysis on marital status, maternal education, gravidity (previous pregnancies), and parity (previous births) was

conducted using χ^2 tests. Descriptive statistics were repeated for data on all pregnancies in the cohort.

Next, bivariate analysis was conducted for each pre-existing conditions or past medical history using χ^2 test or Fischer's exact test for all women. Fischer's exact test was used instead of χ^2 test when expected cell count was below five. This analysis was repeated for all pregnancies.

The crude relationships between pregnancy complications (transient hypertension, mild preeclampsia, severe preeclampsia or eclampsia, abnormal glucose tolerance, gestational diabetes, and other complications including anemia, thyroid disorders, and vaginal and urinary tract infections) and AMA were evaluated. The younger age group (35-39) was used as the reference group for all analyses to compare the risk of outcomes in the AMA group. Crude risk ratios (cRR), 95% confidence intervals (CI), χ^2 test statistics, degrees of freedom, and p-values were calculated using log binomial regression and χ^2 or Fischer's exact tests.

Next, the adjusted relationships between pregnancy complications and AMA were assessed using log-binomial regression. The regression adjusted for potential confounders and correlation among multiple pregnancies of the same women using generalized estimated equations approach with autoregressive correlation structure. The choice of the correlation structure did not significantly alter effect estimates due to the small proportion of correlated data in this dataset. If the model failed to converge, Poisson distribution was used instead of the binomial distribution to approximate the risk ratio. If the model still failed to converge, less important variables were dropped from the model. Adjusted risk ratios (aRR), 95% confidence intervals (CI), Score test, and p-values were reported.

Potential confounders considered included obesity, maternal race, marital status, gravidity, and history of infertility. All potential confounders and interaction terms were included in the starting model. Condition indexes greater than 30, and variance decomposition proportions greater than 0.5 were indicative of collinearity, and higher order variables were excluded from the model one by one until there was no collinearity problem in the model. Interaction terms of the

variables in the model were considered using likelihood ratio tests. Confounders were left in the final model if the risk ratio for the primary exposure variable changed more than 10% when that variable was excluded form the model, or if they were regarded as important confounders in previous literature.

Although pregnancy outcomes were not the primary focus of this study, major pregnancy outcomes of the entire cohort of 2167 pregnancies, including pregnancies without BC data, were compared across two age groups by obtaining crude risk ratios. These outcomes included spontaneous abortion, induced abortion, other abnormal pregnancies not resulting in birth, cesarean sections among women who delivered live births, and preterm birth among women with BC data. Fetal death was not investigated in this study due to lack of information regarding fetal outcomes from maternal KPGA medical records and BC data.

Crude association of potential risk factors/confounders and the following outcomes were evaluated using χ^2 tests 1) any hypertensive complications (includes chronic hypertension, transient hypertension, preeclampsia, and eclampsia), 2) transient hypertension, 3) preeclampsia/eclampsia, 4) any diabetic complications (pre-existing diabetes mellitus and gestational diabetes) and 5) gestational diabetes. Potential risk factors included obesity, maternal race, marital status, maternal education, history of infertility (ovarian dysfunction, menopause, or use of infertility-related drugs), history of hypertensive or diabetic disorders, concurrent hypertensive or diabetic complications, and history of thyroid, autoimmune, and hypercoagulative disorders. Next, risk factors that appeared to be associated with the five outcomes were selected as variables to be added into the starting log-risk regression model. Using all possible subsets approach, various regression models were compared in order to obtain the most unbiased, simplified model with the narrowest confidence interval. Final model was checked for multicollearity. QIC (Quasilikelihood under the Independence model Criterion) was evaluated. From the final model, estimated effect estimates for AMA were obtained, and compared against other risk factors.

III. Results

This retrospective cohort study included a total of 2167 pregnancies from 1977 women, with the majority of the analysis performed among a subset of women (1181 pregnancies from 1096 women) with linked Georgia BC data. The demographic characteristics for 1096 women and for 1181 pregnancies by these women at the time of their FOB visit are shown in Table 1A and 1B. The demographic characteristics for all 2167 pregnancies of 1969 women, including women with and without linked BC data, are shown in the Appendices (Appendix 1A, 1B). The study population consisted of 1096 pregnant women between the ages 35 and 46 at the time of their FOB visit. The younger reference group (ref) consisted of 939 (85.6%) women between the ages 35 and 39, with the mean age of 36.4 years old (SD±1.3), and the AMA group consisted of 157 (14.3%) women who were 40 years and older, with a mean average of 41.2 years old (±1.5). The mean gestational age at FOB was 8.2 (±1.7) weeks for the younger group, and 8.7 (±1.7) weeks for the AMA group (p=0.01). Of the 1017 women who had pre-pregnancy weight and height measurements, the mean pre-pregnancy BMI was 27.3 kg/m^2 (±6.2), and 22.0%(n=241) were obese. There were higher proportion of black and African American women in the advanced maternal group compared to the younger reference group (ref: 41.7%, AMA: 53.5%), but both groups had similar proportion of Asian women (ref: 11.4% Blacks, AMA: 8.9% Blacks). Although the proportion of unmarried women were higher in the advanced age group, the result was not statistically significant (χ^2 =3.09, p=0.079). Among 1096 women with linked BC data, there were 834 women with previous pregnancies. There were no significant differences in the level of education, previous pregnancies (gravidity), and previous births (parity) across the two age groups.

Tables 2A and 2B represent the distribution of pre-existing medical conditions and past medical history by maternal age groups for 1096 women in the study who had linked BC data (Table 2A), and for 1181 pregnancies in the study (Table 2B). Data for all 2167 pregnancies of 1969 women are shown in the Appendices (Appendix 2A, 2B). The risk of having chronic

hypertension was higher in the AMA group compared to the younger group ($p<0.001$), but there were no significant differences for history of chronic diabetes mellitus ($p=0.72$, Table 2A). The proportion of women with history of infertility and bacterial vaginosis were higher in the AMA group compared to the younger age group.

Among 834 women in the study who have been pregnant prior to this study, pregnancy-related histories were compared across age groups (Table 3). There were no significant differences across age groups regarding the history of transient hypertension, preeclampsia/eclampsia, and gestational diabetes in previous pregnancies. History of cesarean sections and abortion in previous pregnancies were also similar across age groups.

Risk of having any hypertensive complications including chronic hypertension, transient hypertension, mild preeclampsia, severe preeclampsia, or eclampsia was significantly higher among the AMA group (crude risk ratio [cRR], 1.51; 95% confidence interval [CI], 1.18-1.95), but this association was predominantly caused by higher risk of chronic hypertension among the AMA group (cRR, 1.95; 95%CI, 1.34-2.84, Table 4A). Risk of transient hypertension (cRR, 1.38; 95%CI, 0.77-2.46), and preeclampsia/eclampsia were not significantly different across the age groups (cRR, 1.10; 95%CI, 0.59-2.05). For diabetic complications, risk of having any diabetic complications (chronic diabetes or gestational diabetes) did not differ by age groups (cRR, 0.96; 95%CI, 0.66-1.40). Neither the risk of chronic diabetes (cRR, 0.89; 95% CI, 0.49-1.61) nor gestational diabetes (cRR, 1.01; 95% CI, 0.64-1.60) was significantly higher in the AMA group. The risk of anemia, bacterial vaginosis, candidiasis, and urinary tract infections were more elevated in the AMA group, but the differences were not statistically significant. Similar results were obtained when all 2167 pregnancies of 1969 women were used (Appendix 3).

Results were similar when risk ratios were adjusted for maternal race, obesity, infertility, gravidity, marital status, and correlation among multiple pregnancy data from the same mother (Table 4B). These covariates were confounders in at least one of the relationships between AMA

and pregnancy complications. Risk of any hypertensive complication (adjusted risk ratio [aRR], 1.55; 95%CI, 1.19-2.01) and chronic hypertension (aRR 2.05; 95%CI, 1.48-2.86), were significantly higher among AMA group but risk of transient hypertension (aRR, 1.07; 95%CI, 0.51-2.22), mild preeclampsia (aRR 1.31; 95%CI, 0.61-2.81), severe preeclampsia/eclampsia (aRR 0.87; 95%CI, 0.26-2.86), chronic diabetes (aRR 0.74; 95%CI, 0.37-1.50), and gestational diabetes (aRR 0.97; 95%CI, 0.59-1.59) were not significantly different across the age groups.

The outcome of all pregnancies in the cohort is shown in Table 5. Risk of spontaneous abortion was significantly higher among older mothers (cRR, 1.96; 95%CI 1.58-2.44), and risk of abnormal pregnancies such as molar and ectopic pregnancies were also higher for older mothers (cRR1.48; 95%CI 1.08-2.01). In our cohort, risk of cesarean section did not differ across age groups among 1797 live births in the cohort of 2167 pregnancies (p=0.85).

A list of potential risk factors was assessed for their crude association with the three major outcomes of interest: any hypertensive complications during pregnancy (includes chronic hypertension, transient hypertension, preeclampsia, or eclampsia), transient hypertension, preeclampsia/eclampsia, any diabetic complications during pregnancy (chronic diabetes and gestational diabetes), and gestational diabetes (Tables 6-10).

AMA, obesity, maternal race, primigravida, and history of hypertensive complications in previous pregnancies (transient hypertension, preeclampsia, and eclampsia) were independently associated with any hypertensive complications during pregnancy (Table 6). Black of African American maternal race was associated with higher risk of hypertensive complications ($p<0.001$), whereas Asian maternal race was associated with decreased risk (p=0.03).

Although the relationship was not statistically significant, mothers with history of hypercoagulative disorders, autoimmune disorders, and history of transient hypertension in previous pregnancies, had elevated risks for transient hypertension (Table 7).

For preeclampsia/eclampsia (Table 8), significant risk factors were obesity (p=0.03), maternal race (p=0.01), and marital status (p=0.002). In particular, black race appeared to be

significantly associated with higher risk of preeclampsia/eclampsia compared to white race ($p=0.014$). Unmarried mothers also had significantly higher risk of preeclampsia/eclampsia compared to married mothers ($p=0.002$). History of chronic hypertension ($p<0.001$) and history of preeclampsia/eclampsia in previous pregnancies ($p=0.003$) were also associated with increased risk for preeclampsia/eclampsia.

Obesity, maternal race, maternal education, primigravida, history of chronic hypertension, and gestational diabetes were independently associated with diabetic complications during pregnancy (including chronic diabetes and gestational diabetes) (Table 9). Both black and Asian maternal race were associated with higher risk.

For gestational diabetes (Table 10), being obese ($p=0.004$), primigravid ($p=0.006$), or of Asian race ($p<0.001$) were significantly associated with increased risk for gestational diabetes. History of gestational diabetes in previous pregnancies was also associated with gestational diabetes ($p<0.001$). Graduate-level education such as completion of a master's degree or a doctorate degree was significantly associated decreased risk of gestational diabetes ($p=0.03$). History of hypertensive disorders such as chronic hypertension, transient hypertension, and preeclampsia/eclampsia, did not appear to be associated with gestational diabetes.

Using potential confounders and risk factors from previous studies, log-Binomial regression model was constructed to estimate the risk ratios of the association between AMA and pregnancy complications (transient hypertension, preeclampsia/eclampsia, and gestational diabetes), adjusted for correlation among multiple pregnancies of the same women using autoregressive correlation structure. When log-Binomial regression model did not converge, log-Poisson regression was used to approximate the risk ratio.

Amongst the five regression models, AMA was a significant risk factor in only the log-Poisson regression model for estimating the log risk of any hypertensive complications including chronic hypertension, transient hypertension, preeclampsia, and eclampsia.

1) Log-Poisson regression model for any hypertensive complications

Log-Poisson regression model was fit for any hypertensive complications, which included chronic hypertension, transient hypertension, and preeclampsia/eclampsia. The starting full model included AMA, history of chronic diabetes, obesity, primigravida, maternal race, infertility, and marital status. Using all possible subsets approach, the best model with least variables and narrowest confidence interval included obesity, history of chronic diabetes, primigravida, and maternal race as confounders in the relationships between AMA and any hypertensive complications. Infertility and marital status were dropped from the model without affecting the effect estimate of AMA by over 10%. The final model did not have any collinearity problems, and QIC statistic for the model was 1353.

According to the final model, even after adjusting for obesity, history of diabetes mellitus, primigravida, and maternal race, AMA was significantly associated with any hypertensive complications during pregnancy (Score test: 8.93, $p=0.003$). Obesity (Score test: 31.67, $p<0.001$), history of diabetes mellitus (Score test: 3.79, $p=0.05$), primigravida (Score test: 11.74, $p=0.001$), and Black race (Score test: 7.89, $p=0.005$) were significant risk factors for hypertensive complications (Table 11).

Data was stratified by white and black maternal race, in order to see whether AMA was a significant risk factor for both races. Stratified regression models for estimating the log risk of any hypertensive complications were obtained for white and black maternal race (Table 12, 13). When two separate regression models were fit for predicting the risk of any hypertensive complications, AMA was a significant risk factor among blacks ($p=0.005$), but not among mothers of white race ($p=0.103$). Primigravida ($p=0.045$) and obesity ($p=0.001$) were also significant risk factors for hypertensive complications among blacks, but obesity was the only significant risk factor for hypertensive complications in mothers of white maternal race ($p<0.001$).

2) Log-Binomial regression model for transient hypertension

The starting full model for transient hypertension included AMA as primary exposure of interest, with obesity, history of diabetes mellitus, gravidity, maternal race, infertility, marital status, history of hypercoagulative disorders as potential confounders. Interaction terms with AMA and other risk factors/confounders (obesity, any diabetic complications, gravidity, infertility, marital status, maternal education) were all insignificant and dropped from the model. Marital status was dropped from the model, as it did not change the beta coefficient for AMA by over 10%.

Therefore, AMA (Score test: 0.04, p=0.845) was not a significant risk factor for transient hypertension in the final model with obesity, history of diabetes mellitus, primigravida, maternal race, infertility, and history of hypercoagulative disorders as confounders (Table 14). The final model did not have any collinearity problems, and QIC statistic for the model was 421.

3) Log-Poisson regression model for preeclampsia/eclampsia

The starting full model for preeclampsia/eclampsia included AMA as the primary exposure of interest, with obesity, primigravida, marital status, maternal race, infertility, history of diabetes mellitus, and history of chronic hypertension. Using all possible subsets approach, obesity, primigravida, infertility, and history of diabetes mellitus were dropped from the model, dropping them did not change the effect estimate for AMA by over 10%. Marital status, maternal race, and history of chronic hypertension were important confounders in the relationship between AMA and preeclampsia/eclampsia, and could not be dropped from the model.

Therefore, the final model contained AMA, history of chronic hypertension (HTN), marital status, and maternal race (Table 15). The final model did not have any collinearity problems, and QIC statistic for the model was 502. According to the final model, AMA was not a significant risk factor for preeclampsia/eclampsia. Instead, having a history of chronic hypertension significantly increased the risk of preeclampsia/eclampsia when maternal age group,

marital status, and maternal race were adjusted for ($p<0.001$). The risk of preeclampsia/eclampsia appeared to be lower among Asians compared to whites, but this difference was not statistically significant ($p=0.09$).

4) Log-Poisson regression model for any diabetic complications during pregnancy

Log-Poisson regression model for any diabetic complications during pregnancy, which included diabetes mellitus and gestational diabetes, was fit. The starting model included AMA as the primary exposure of interest, obesity, primigravida, infertility, maternal education, marital status, maternal race, and history of chronic hypertension. However, the model failed to converge until only AMA, obesity, and maternal race were left in the model. Obesity and maternal race could not be dropped from the model as they changed the effect estimate for AMA by over 10%. The final model did not have any collinearity problems, and QIC statistic for the model was 1136.

In the final model, AMA did not significantly increase the risk of having any diabetic complications during pregnancy, when obesity and maternal race are adjusted for in the model (Table 16). However, Asian maternal race ($p=0.002$) or other race ($p<0.001$) including American Indian, Alaskan Native, multiracial, or unknown race, were significantly associated with increased risk for any diabetic complications during pregnancy. When data was further stratified by white and Asian maternal race, obesity remained a significant risk factor for whites ($p=0.002$, Table 17), but not among Asians ($p=0.5587$, Table 18).

5) Log-Poisson regression model for gestational diabetes

The starting full model for gestational diabetes included AMA as the primary exposure of interest, with obesity, primigravida, infertility, maternal race, marital status, maternal education, and history of chronic hypertension as risk factors of interest. History of infertility, marital status, maternal education, and history of chronic hypertension were dropped from the full model, as the model failed to converge when these variables were included in the model. Obesity, primigravida, and maternal race were kept in the model, as they altered the effect estimate for

AMA by over 10%. Therefore, the full model contained AMA, obesity, primigravida, and maternal race (Table 19). The final model did not have any collinearity problems, and QIC statistic for the model was 749.

In the final model, AMA was not a significant risk factor for gestational diabetes when obesity, primigravida, and maternal race were adjusted for ($p= 0.85$). However, obesity ($p<0.01$), primigravida ($p<0.01$), and Asian maternal race ($p<0.001$), were significantly associated with increased risk of gestational diabetes.

IV. Discussion

The primary objective of this study was to assess whether women who become pregnant at an advanced age (40 years and above at the time of their first obstetrics/prenatal visit) were at a higher risk of hypertensive and diabetic complications during pregnancy compared to younger mothers (women between the ages 35 and 39 at the time of their first obstetrics/prenatal visit). Women of AMA had a two-fold risk of having chronic hypertension compared to the younger reference group, but AMA was not a significant risk factor for transient hypertension, preeclampsia/eclampsia, chronic diabetes, and gestational diabetes.

The secondary objective was to investigate whether AMA or other risk factors more fully explained the risk of hypertensive and diabetic complications. For any hypertensive disorders during pregnancy, AMA remained a significant risk factor even after adjusting for obesity, gravidity, maternal race, and history of chronic diabetes. This was consistent with studies by Koo et al. (40), where risk of chronic hypertension was significantly higher among women who were 40 years and older compared to younger women (20-29 years old), and hypertensive complications (gestational hypertension, preeclampsia, eclampsia) were also significantly increased among women over 40 compared to younger women after adjusting for gravidity, parity, BMI, history of spontaneous abortion, history of *in vitro* fertilization, and pre-existing

medical conditions. Obesity, black maternal race, and primigravida were also significant risk factors for hypertensive complications.

When analysis was stratified by white and black race, both AMA and obesity were found to be significant risk factors for hypertensive complications among blacks, but only obesity and not AMA was a significant risk factor for whites. This may suggest that there are racial/ethnic differences in the effects of AMA on hypertensive outcomes, but further investigations are required to show this relationship.

For transient hypertension, neither AMA nor other risk factors (obesity, history of chronic diabetes, primigravida, maternal race, infertility, and history of hypercoagulative disorders) were significant risk factors. This finding was similar to the study by Cleary-Goldman et al. (41) where risk of transient hypertension was not higher for AMA mothers, even after maternal race, parity, BMI, maternal education, marital status, smoking, pre-existing medical conditions, previous adverse pregnancy outcomes, and use of assisted conception were adjusted for. This study outcome was similar to studies of Ludford et al. (42) and Cleary-Goldman et al. (41), where there was increase in risk of chronic hypertension for the AMA group, but there was no increase in risk of transient hypertension. The prevalence of transient hypertension in this study (4.5% in the reference group and 5.1% in the AMA group) was also similar to findings of Cleary-Goldman et al. (41), which reported 4.7% prevalence of transient hypertension in the younger reference group (<35 years old) and 5.5% in the AMA group (≥40 years old and over). Two other population-based cohort studies also did not find significant association between AMA and transient hypertension (42, 43). However, there are also other population-based studies (12, 44, 45) and small cohort studies (46-48) that have found significant association between AMA and transient hypertension, and the association remains inconclusive.

AMA was also not a significant risk factor for mild preeclampsia or severe preeclampsia/eclampsia, after adjusting for history of chronic hypertension, marital status, and maternal race. Although the relationship was not significant, risk of mild preeclampsia was

mildly elevated in the AMA group, whereas severe eclampsia and eclampsia were slightly elevated among younger mothers. This was contrary to the findings by Jacobsson et al. (12) who found that mild preeclampsia was more likely to occur in the younger group (age 20 to 29) compared to the AMA group (age ≥45), and severe preeclampsia was more likely to occur in the advanced age group compared to the younger group after adjusting for parity, marital status, smoking status, history of malformation and maternal diseases, and multiple pregnancies. There are two other studies that have investigated the effects of AMA separately for mild and severe preeclampsia, but contrary to findings in this study, both studies have found significant increase in risks for both mild and severe preeclampsia in the AMA group (49, 50).

In this study, unmarried marital status and history of chronic hypertension were significant risk factors for having either preeclampsia or eclampsia. Obesity was a significantly associated with preeclampsia/eclampsia, but was dropped from the model as it was not a confounder when maternal race, history of chronic diabetes, and marital status were adjusted for in the regression model. This was inconsistent with previous studies where obesity have been found to be an independent factor for preeclampsia, even when maternal age, parity, chronic hypertension were adjusted for (51).

The results of this study was consistent with findings by Cleary-Goldman et al. (41), where AMA of 35 and above did not significantly increase the risk of preeclampsia when maternal race, parity, BMI, education, marital status, smoking, and pre-existing medical conditions, previous adverse pregnancy outcome, and use of assisted conception were adjusted for in the model. Study by Wang et al. (52) that used the same age categorization for AMA and reference group as this study also did not find significant association between AMA and preeclampsia. Prevalence of preeclampsia and eclampsia in this study was also consistent with previous studies conducted in the US that had similar demographical characteristics (53, 54).

Contrary to findings in this study, there are many small cohort studies that have found AMA to be a significant risk factor for preeclampsia/eclampsia, few of these studies have

adjusted for potential confounders in their analysis. One of these is a study by Bianco, et al. (9) that showed significant increase in risk for preeclampsia in the AMA group (age ≥40) compared to the reference group (age 20-29), even after adjusting for parity, pre-pregnancy weight, maternal race, tobacco use, and medical history, which included history of chronic hypertension, preeclampsia, and diabetes.

For any diabetic complications during pregnancy, maternal race was the most important risk factor compared to AMA. AMA was also not a significant risk factor for gestational diabetes compared to obesity, maternal race, and primigravida. Asians had a significantly higher risk of diabetic complications compared to whites, and when the cohort was stratified by white and Asian race, obesity was a significant risk factor among only whites, but not among Asians. An interesting study by Hedderson et al. (55) showed that age-adjusted prevalence of gestational diabetes increased as BMI increased, but the association differed by ethnic/racial groups. In this study, Asians had a higher risk of gestational diabetes even at low BMI-levels compared to other racial groups. The decision to use BMI of 30 and over as cut-off value for obesity, may have caused obesity to become insignificant in the analysis for gestational diabetes among Asians.

Although prevalence of gestational diabetes differ by types of diagnostic criteria used at different times and in different regions across the world, gestational diabetes is known to affect roughly 1.7% to 11.6% of pregnancies in high-income countries (56), and the prevalence of 9.5% observed in this study was consistent with previous literature.

As studies on the association of insulin-resistance and hypertensive complications of pregnancy have shown (34-36), results of this study also showed that hypertensive and diabetic pregnancy complications share common risk factors such as obesity, maternal race, and history of chronic conditions. Chronic diabetes was an important risk factor for hypertensive complications of pregnancy ($p=0.05$), but chronic hypertension did not appear to be an important risk factor for diabetic pregnancy complications.

Strengths

Few studies have investigated the effects of AMA in relation to other commonly known risk factors of hypertensive and diabetic pregnancy complications. This study was able to investigate relative contribution AMA compared to other risk factors separately for any hypertensive complications during pregnancy, transient hypertension, preeclampsia/eclampsia, any diabetic complications, and gestational diabetes by modeling these outcomes separately and adjusting for potential confounders. Another strength of this study lies in the availability of information on patient characteristics and pre-existing conditions that were obtained by KPGA medical records and BC data. Additionally, the study population had large proportion of Blacks and Asians compared to other studies on AMA conducted in the US (41, 44, 47). Adequacy of prenatal care was adjusted for in the study, since all women had to be enrolled in KPGA health plan throughout their pregnancy, in order to be enrolled in the study.

Limitations

A major limitation of this study was the possibility of misclassification error due to the retrospective nature of the study. Hypertensive history and complications were determined from seven ICD-9-CM codes from KPGA medical records, and diabetic history and complications were derived from four diagnosis codes from KPGA medical records. The dates in which these codes were entered into patient medical records were used to determine whether the diagnosis was categorized as pre-existing or occurring during pregnancy. For instance, when a patient had an ICD-9-CM code for transient hypertension during the first 20 weeks of pregnancy, they were re-categorized as having chronic hypertension since transient hypertension was defined as hypertension developing after 20 weeks of gestation. As a consequence, misclassification could have occurred due to inconsistencies in the choice of ICD-9 codes entered in the clinical setting.

Another major limitation was the high proportion of women in the study without linked Georgia BC data. Of the 1797 live births in a cohort of 2167 pregnancies, 34.3% (616

pregnancies) had missing BC data, and were excluded from the majority of analysis done in this study due to lack of information on gravidity, education, and marital status. This also contributed to another limitation in this study, which was small sample size. A larger sample size would have yielded narrower confidence intervals, which may have changed some of the study outcomes. Additionally, information on parity and gravidity were only available through BC data, which may have lacked accuracy.

Previous meta-analysis studies have found that assisted reproductive technology (ART) conceived pregnancies have higher risk of hypertensive complications (57). In addition, women with PCOS have also been known to have higher risk of hypertensive complications during pregnancy even after accounting for use of ART, maternal age, obesity, parity, maternal education, cigarette use, and year of delivery (58). In this study, women who have been diagnosed with ovary dysfunctions, menopause, or have had medication dispensing history of infertility-related drugs were categorized as having history of infertility. Therefore, women of varying degrees of infertility were included among those with history of infertility, which may explain why infertility was not an important risk factor in our study. Information on the use of artificial reproductive technologies (ART) or use of donated eggs for conception was not available in this study, but may have been important confounders during the analysis.

Lastly, this study lacked information on delivery logs and infant medical records, which limited the ability to evaluate delivery complications and fetal outcomes. The study also lacked information on smoking status of mothers during pregnancy and use of ART for conception, which may have been important risk factors in this study.

Future directions

Results of this study showed that while the risk of chronic hypertension was significantly higher among women of advanced age, other risk factors such as obesity, maternal race, gravidity, and medical history appeared to play a larger role in the development of preeclampsia,

eclampsia, and gestational diabetes. Hypertensive and diabetic complications of pregnancy share common risk factors, but the strength of association of these risk factors may vary depending on the race/ethnicity of the mother. Further studies are required to understand how different race/ethnicity groups have different risk profiles. Based on this study, it is recommended that health professionals pay attention to not just one risk factor such as age, but to a combination of risk factors, keeping in mind that one risk factor may have different strengths of influence depending on the ethnic profile and its association with other risk factors.

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Tables

Table 1A. Characteristics of women by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB), who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, and whose medical records were linked to Georgia Birth Certificate data (n=1096)[a]

Characteristics	Total		≥ 35		35 - 39		≥ 40		χ2	df	p-value	
	(n = 1096)		(n = 939)		(n = 157)							
Maternal age (years) at FOB, mean (±SD)	37.1 (±2.14)		36.4 (±1.32)		41.2 (±1.46)							
Gestational age (weeks) at FOB, mean (±SD)[b]	8.3 (±1.68)		8.2 (±1.65)		8.7 (±1.80)				-3.23	1094	0.001	*
Prepregnancy BMI, median (±SD)[b]	27.3 (±6.17)		27.4 (±6.18)		27.3 (±6.13)				0.17	1015	0.869	
Unknown, n %	79	7.2	69	7.3	10	6.4						
Obesity, n %												
Not Obese	629	57.4	629	67.0	110	70.1			0.41	1	0.524	
Obese	241	22.0	241	25.7	37	23.6						
Unknown	79	7.2	69	7.3	10	6.4						
Race, n %												
Black/African American	477	43.5	393	41.9	84	53.5			7.49	3	0.058	
White	444	40.5	392	41.7	52	33.1						
Asian	121	11.0	107	11.4	14	8.9						
Other[c]	54	4.9	47	5.0	7	4.5						
Marital Status, n %												
Married	949	86.6	820	87.3	129	82.2			3.09	1	0.079	
Not Married	147	13.4	119	12.7	28	17.8						
Education, n %												
Less than 8th grade	17	1.6	15	1.6	2	1.3			2.55	3	0.466	
9th grade to High School Diploma	142	13.0	116	12.4	25	15.9						
Some college to Bachelor Diploma	642	58.6	542	57.7	99	63.1						
Masters and beyond	152	13.9	132	14.1	17	10.8						
Missing	149	13.6	134	14.3	14	8.9						
Previous pregnancies, n %												
No	262	23.9	219	23.3	43	27.4			1.22	1	0.269	
Yes	834	76.1	720	76.7	114	72.6						
Previous births, n %												
No	346	31.6	290	30.9	56	35.7			1.43	1	0.233	
Yes	750	68.4	649	69.1	101	64.3						

[a]If women had multiple FOB visits, data from the earliest FOB visit for each women was included

[b]Pooled two sample t-test and t-test statistics

[c]Other includes other racial groups (n=24) consisting of American Indian, Alaskan Native, Multiracial, and unknown race (n=30) There were no Native Hawaiian or Pacific Islanders

*Statistical significance at alpha=0.05

Table 1B. Characteristics of women by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB), who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, and whose medical records were linked to Georgia Birth Certificate data, including multiple pregnancies by the same women during the study period (n=1181)[a]

Characteristics	Total		≥ 35		35 - 39		≥ 40		χ2	df	p-value	
	(n = 1181)		(n = 1003)		(n = 178)							
Maternal age at FOB, mean (±SD)	37.20 (±2.13)		36.50 (±1.34)		41.23 (±1.41)							
Gestational age at FOB, mean (±SD)[b]	8.25 (±1.67)		8.18 (±1.64)		8.63 (±1.81)				-3.35	1179	0.001	*
Prepregnancy BMI, median (±SD)[b]	27.36 (±6.14)		27.35 (±6.15)		27.42 (±6.10)				-0.14	1094	0.892	
Unknown, n %	85	7.2	74	7.4	11	6.2						
Obesity, n %												
Not Obese	790	66.9	666	66.4	124	69.7			0.46	1	0.497	
Obese	306	25.9	263	26.2	43	24.2						
Unknown	85	7.2	74	7.4	11	6.2						
Race, n %												
Black/African American	509	43.1	415	41.4	94	52.8			8.47	3	0.037	*
White	484	41.0	422	42.1	62	34.8						
Asian	130	11.0	116	11.6	14	7.9						
Other[c]	58	4.9	50	5.0	8	4.5						
Marital Status, n %												
Married	1030	87.2	882	87.9	148	83.1			3.11	1	0.078	
Not Married	151	12.8	121	12.1	30	16.9						
Education, n %												
Less than 8th grade	17	1.4	15	1.5	2	1.1			3.68	3	0.298	
9th grade to High School Diploma	155	13.1	126	12.6	29	16.3						
Some college to Bachelor Diploma	692	58.6	580	57.8	112	62.9						
Masters and beyond	159	13.5	141	14.1	18	10.1						
Missing	158	13.4	141	14.1	17	9.6						
Previous pregnancies, n %												
No	268	22.7	222	22.1	46	25.8			1.19	1	0.276	
Yes	913	77.3	781	77.9	132	74.2						
Previous births, n %												
No	359	30.4	299	29.8	60	33.7			1.09	1	0.298	
Yes	822	69.6	704	70.2	118	66.3						

[a]χ2 tests and t-tests are not adjusted for correlation among women with multiple pregnancies

[b]Pooled two sample t-test and t test statistics

[c]Other includes other racial groups (n=26) consisting of American Indian, Alaskan Native, Multiracial, and unknown race (n=32) There were no Native Hawaiian or Pacific Islanders

*Statistical significance at alpha=0.05

Table 2A. Pre-existing conditions and past medical history by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB) for both primigravid and multigravid women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, and whose medical records were linked to Georgia Birth Certificate (n=1096)[a]

History	Total ≥ 35 (n = 1096)		35 - 39 (n = 939)		≥ 40 (n = 157)		χ2	df	p-value	
Pre-existing hypertension										
No	978	89.2	853	90.8	125	79.6	17.64	1	< 0.001	*
Yes	118	10.8	86	9.2	32	20.4				
Pre-existing diabetes mellitus										
No	1026	93.6	878	93.5	148	94.3	0.13	1	0.717	
Yes	70	6.4	61	6.5	9	5.7				
History of other diseases										
Depression										
No	955	87.1	818	87.1	137	87.3	0.00	1	0.959	
Yes	141	12.9	121	12.9	20	12.7				
Seizure disorders[c]										
No	1093	99.7	936	99.7	157	100.0	-	-	1	
Yes	3	0.3	3	0.3	0	0.0				
Thyroid disorders										
No	1010	92.2	867	92.3	143	91.1	0.29	1	0.590	
Yes	86	7.8	72	7.7	14	8.9				
Autoimmune disorders[c]										
No	1082	98.7	929	98.9	153	97.5	-	-	0.128	
Yes	14	1.3	10	1.1	4	2.5				
Hypercoagulative disorders[c]										
No	1095	99.9	938	99.9	157	100.0	-	-	1	
Yes	1	0.1	1	0.1	0	0.0				
Deep vein thrombosis[c]										
No	1092	99.6	935	99.6	157	100.0	-	-	1	
Yes	4	0.4	4	0.4	0	0.0				
Pulmonary embolism[c]										
No	1095	99.9	939	100.0	156	99.4	-	-	0.143	
Yes	1	0.1	0	0.0	1	0.6				
Infertility[d]										
No	907	82.8	793	84.5	114	72.6	13.21	1	< 0.001	*
Yes	189	17.2	146	15.5	43	27.4				
Bacterial vaginosis										
No	778	71.0	679	72.3	99	63.1	5.59	1	0.018	*
Yes	318	29.0	260	27.7	58	36.9				
Candidiasis										
No	939	85.7	798	85.0	141	89.8	2.55	1	0.110	
Yes	157	14.3	141	15.0	16	10.2				
Urinary tract infection										
No	864	78.8	749	79.8	115	73.2	3.42	1	0.064	
Yes	232	21.2	190	20.2	42	26.8				

Data are expressed as n %

[a]If women had multiple FOB visits, data from the earliest FOB visit for each women was included

[b]Any glucose intolerance includes chronic diabetes or abnormal glucose test result unrelated to pregnancy

[c]Fischer's exact test

[d]History of infertility includes ovary dysfunction, menopause, and history of infertility medication use

* Statistical significance at alpha=0.05

Table 2B. Pre-existing conditions and past medical history by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of their first obstetrics/prenatal visit (FOB) for both primigravid and multigravid women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, and whose medical records were linked to Georgia Birth Certificate data, including multiple pregnancies by the same women during the study period (n=1181)[a]

History	Total ≥ 35 (n = 1181)		35 - 39 (n = 1003)		≥ 40 (n = 178)		χ2	df	p-value	
Pre-existing hypertension										
No	1050	88.9	909	90.6	141	79.2	19.97	1	< 0.001	*
Yes	131	11.1	94	9.4	37	20.8				
Pre-existing diabetes mellitus										
No	1107	93.7	939	93.6	168	94.4	0.15	1	0.699	
Yes	74	6.3	64	6.4	10	5.6				
History of other diseases										
Depression										
No	1022	86.5	868	86.5	154	86.5	0.0001	1	0.993	
Yes	159	13.5	135	13.5	24	13.5				
Seizure disorders[c]										
No	1177	99.7	999	99.6	178	100.0	-	-	1	
Yes	4	0.3	4	0.4	0	0.0				
Thyroid disorders										
No	1089	92.2	926	92.3	163	91.6	0.12	1	0.731	
Yes	92	7.8	77	7.7	15	8.4				
Autoimmune disorders[c]										
No	1166	98.7	992	98.9	174	97.8	-	-	0.263	
Yes	15	1.3	11	1.1	4	2.2				
Hypercoagulative disorders[c]										
No	1179	99.8	1001	99.8	178	100.0	-	-	1	
Yes	2	0.2	2	0.2	0	0.0				
Deep vein thrombosis[c]										
No	1177	99.7	999	99.6	178	100.0	-	-	1	
Yes	4	0.3	4	0.4	0	0.0				
Pulmonary embolism[c]										
No	1180	99.9	1003	100.0	177	99.4	-	-	0.151	
Yes	1	0.1	0	0.0	1	0.6				
Infertility[d]										
No	969	82.0	839	83.6	130	73.0	11.57	1	0.001	*
Yes	212	18.0	164	16.4	48	27.0				
Bacterial vaginosis										
No	831	70.4	719	71.7	112	62.9	5.57	1	0.018	*
Yes	350	29.6	284	28.3	66	37.1				
Candidiasis										
No	1011	85.6	856	85.3	155	87.1	0.37	1	0.544	
Yes	170	14.4	147	14.7	23	12.9				
Urinary tract infection										
No	924	78.2	795	79.3	129	72.5	4.09	1	0.043	*
Yes	257	21.8	208	20.7	49	27.5				

Data are expressed as n %

[a]χ2 tests are not adjusted for correlation among women with multiple pregnancies

[b]Any glucose intolerance includes chronic diabetes or abnormal glucose test result unrelated to pregnancy

[c]Fischer's exact test

[d]History of infertility includes ovary dysfunction, menopause, and history of infertility medication use

* Statistical significance at alpha=0.05

Table 3. Pre-existing conditions and past medical history by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB) for multigravid women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data (n=834)[a]

Obstetrical History	Total ≥ 35 (n = 834)		35 - 39 (n = 720)		≥ 40 (n = 114)		χ2	df	p-value	
Hypertensive history										
Any hypertensive history[b]										
No	735	88.1	646	89.7	89	78.1	12.77	1	< 0.001	*
Yes	99	11.9	74	10.3	25	21.9				
Chronic hypertension										
No	756	90.6	665	92.4	91	79.8	18.25	1	< 0.001	*
Yes	78	9.4	55	7.6	23	20.2				
Transient hypertension in previous pregnancies[c]										
No	823	98.7	710	98.6	113	99.1	-	-	1	
Yes	11	1.3	10	1.4	1	0.9				
Preeclampsia or eclampsia in previous pregnancies[c]										
No	811	97.2	702	97.5	109	95.6	-	-	0.228	
Yes	23	2.8	18	2.5	5	4.4				
Mild Preeclampsia in previous pregnancies[c]										
No	816	97.8	707	98.2	109	95.6	-	-	0.086	
Yes	18	2.2	13	1.8	5	4.4				
Severe Preeclampsia/Eclampsia in previous pregnancies[c]										
No	829	99.4	715	99.3	114	100.0	-	-	1.000	
Yes	5	0.6	5	0.7	0	0.0				
Diabetic history										
Any glucose intolerance in previous pregnancies[c,d]										
No	779	93.4	673	93.5	106	93.0	0.04	1	0.845	
Yes	55	6.6	47	6.5	8	7.0				
Gestational diabetes mellitus in previous pregnancies[c]										
No	818	98.1	705	97.9	113	99.1	-	-	0.711	
Yes	16	1.9	15	2.1	1	0.9				
Abnormal glucose tolerance in previous pregnancies[c]										
No	821	98.4	707	98.2	114	100.0	-	-	1	
Yes	19	2.3	17	2.4	2	1.8				
History of other complications										
Thyroid disorder complications during previous pregnancies[c]										
No	823	98.7	712	98.9	111	97.4	-	-	0.181	
Yes	11	1.3	8	1.1	3	2.6				
Anemia during previous pregnancies										
No	782	93.8	673	93.5	109	95.6	0.77	1	0.380	
Yes	52	6.2	47	6.5	5	4.4				
Caesarean section										
No	586	70.3	510	70.8	76	66.7	0.82	1	0.366	
Yes	248	29.7	210	29.2	38	33.3				
Spontaneous abortion										
No	719	86.2	627	87.1	92	80.7	3.37	1	0.066	
Yes	115	13.8	93	12.9	22	19.3				
Induced abortion[c]										
No	817	98.0	704	97.8	113	99.1	-	-	0.493	
Yes	17	2.0	16	2.2	1	0.9				

Data are expressed as n %

[a]Among 1096 women with linked birth certificate data, 834 women were multigravid

[b]Any hypertensive history include chronic hypertension, transient hypertension, mild preelcmpsia, severe preeclampsia, and eclampisa

[c]Fischer's exact test

[d]Any glucose intolerance include chronic diabetes or gestational diabetes

*Statistical significance at alpha=0.05

Table 4A. Crude association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy complications of both primigravid and multigravid women, who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data, including multiple gestations by the same women during the study period (n=1181)[a]

Outcome	Total ≥ 35 (n = 1181)		35 - 39 (n = 1003)		≥ 40 (n = 178)		cRR	95% CI		χ2	df	p-value	
Hypertensive complications													
Any hypertensive complications[b]													
No	956	80.9	829	82.7	127	71.3	1	referent					
Yes	225	19.1	174	17.3	51	28.7	1.71	1.28	2.28	12.52	1	< 0.001	*
Chronic hypertension													
No	1050	88.9	909	90.6	141	79.2	1	referent					
Yes	131	11.1	94	9.4	37	20.8	2.10	1.54	2.88	19.97	1	< 0.001	*
Transient hypertension													
No	1127	95.4	958	95.5	169	94.9	1	referent					
Yes	54	4.6	45	4.5	9	5.1	1.11	0.60	2.05	0.11	1	0.737	
Preeclampsia or eclampsia													
No	1118	94.7	951	94.8	167	93.8	1	referent					
Yes	63	5.3	52	5.2	11	6.2	1.17	0.67	2.04	0.30	1	0.586	
Mild pre-clampsia													
No	1141	96.6	971	96.8	170	95.5	1	referent					
Yes	40	3.4	32	3.2	8	4.5	1.34	0.71	2.53	0.79	0	0.376	
Severe pre-clampsia/eclampsia[c]													
No	1158	98.1	983	98.0	175	98.3	1	referent					
Yes	23	1.9	20	2.0	3	1.7	0.86	0.30	2.50	-	-	1	
Diabetic complications													
Any diabetic complications[d]													
No	995	84.3	844	84.1	151	84.8	1	referent					
Yes	186	15.7	159	15.9	27	15.2	0.96	0.66	1.40	0.05	1	0.817	
Chronic diabetes mellitus													
No	1107	93.7	939	93.6	168	94.4	1	referent					
Yes	74	6.3	64	6.4	10	5.6	0.89	0.49	1.61	0.15	1	0.699	
Gestational diabetes													
No	1069	90.5	908	90.5	161	90.4	1	referent					
Yes	112	9.5	95	9.5	17	9.6	1.01	0.64	1.60	0.00	1	0.974	
Other pregnancy complications													
Anemia													
No	975	82.6	837	83.4	138	77.5	1	referent					
Yes	178	15.1	138	13.8	40	22.5	1.37	1.00	1.89	3.68	1	0.055	
Thyroid disorders complicating pregnancy													
No	1102	93.3	935	93.2	167	93.8	1	referent					
Yes	79	6.7	68	6.8	11	6.2	0.92	0.52	1.62	0.09	1	0.768	
Bacterial vaginosis													
No	1115	94.4	952	94.9	163	91.6	1	referent					
Yes	66	5.6	51	5.1	15	8.4	1.55	0.97	2.48	3.20	1	0.074	
Candidiasis													
No	1126	95.3	959	95.6	167	93.8	1	referent					
Yes	55	4.7	44	4.4	11	6.2	1.35	0.78	2.33	1.09	1	0.296	
Urinary tract infections													
No	1117	94.6	952	94.9	165	92.7	1	referent					
Yes	64	5.4	51	5.1	13	7.3	1.38	0.83	2.28	1.45	1	0.228	

Data are expressed as n %

[a]Not adjusted for correlation among women with multiple pregnancies

[b]Any hypertensive complications include chronic hypertension, transient hypertension, mild preeclampsia, severe preeclampsia, and eclampsia

[c]Fischer's exact test

[d]Any diabetic complications include chronic diabetes mellitus, gestational diabetes, and abnormal glucose tolerance test result during pregnancy

95% CI = 95% Confidence intervals

cRR = crude risk ratio

*Statistical significance at alpha=0.05

Table 4B. Adjusted association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy complications of both primigravid and multigravid women, who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, with linked Georgia Birth Certificate data, including multiple gestations by the same women during the study period (n=1181)[a]

Outcome	Total ≥ 35 (n = 1181)		35 - 39 (n = 1003)		≥ 40 (n = 178)		aRR	95% CI		Score test	p-value	
Hypertensive complications												
Any hypertensive complications[b,c]												
No	956	80.9	829	82.7	127	71.3	1	referent				
Yes	225	19.1	174	17.3	51	28.7	1.55	1.19	2.01	8.13	0.004	*
Chronic hypertension[c]												
No	1050	88.9	909	90.6	141	79.2	1	referent				
Yes	131	11.1	94	9.4	37	20.8	2.05	1.48	2.86	11.82	< 0.001	*
Transient hypertension												
No	1127	95.4	958	95.5	169	94.9	1	referent				
Yes	54	4.6	45	4.5	9	5.1	1.07	0.51	2.22	0.03	0.868	
Mild preeclampsia, severe preeclampsia, or eclampsia[c]												
No	1118	94.7	951	94.8	167	93.8	1	referent				
Yes	63	5.3	52	5.2	11	6.2	1.10	0.59	2.05	0.08	0.780	
Mild pre-clampsia[c]												
No	1141	96.6	971	96.8	170	95.5	1	referent				
Yes	40	3.4	32	3.2	8	4.5	1.31	0.61	2.81	0.41	0.524	
Severe pre-clampsia/eclampsia[c,d]												
No	1158	98.1	983	98.0	175	98.3	1	referent				
Yes	23	1.9	20	2.0	3	1.7	0.87	0.26	2.86	0.06	0.805	
Diabetic complications												
Any diabetic complications[c,e,f]												
No	995	84.3	844	84.1	151	84.8	1	referent				
Yes	186	15.7	159	15.9	27	15.2	0.86	0.62	1.21	0.81	0.369	
Chronic diabetes mellitus[f]												
No	1107	93.7	939	93.6	168	94.4	1	referent				
Yes	74	6.3	64	6.4	10	5.6	0.74	0.37	1.50	0.8	0.370	
Gestational diabetes[c]												
No	1069	90.5	908	90.5	161	90.4	1	referent				
Yes	112	9.5	95	9.5	17	9.6	0.97	0.59	1.59	0.02	0.902	
Other pregnancy complications												
Anemia[e]												
No	975	82.6	837	83.4	138	77.5	1	referent				
Yes	178	15.1	138	13.8	40	22.5	1.19	0.88	1.61	1.14	0.286	
Thyroid disorders complicating pregnancy												
No	1102	93.3	935	93.2	167	93.8	1	referent				
Yes	79	6.7	68	6.8	11	6.2	1.00	0.51	1.95	0.00	0.992	
Bacterial vaginosis												
No	1115	94.4	952	94.9	163	91.6	1	referent				
Yes	66	5.6	51	5.1	15	8.4	1.14	0.63	2.09	0.18	0.674	
Candidiasis												
No	1126	95.3	959	95.6	167	93.8	1	referent				
Yes	55	4.7	44	4.4	11	6.2	1.38	0.72	2.67	0.76	0.384	
Urinary tract infections[c]												
No	1117	94.6	952	94.9	165	92.7	1	referent				
Yes	64	5.4	51	5.1	13	7.3	1.29	0.70	2.38	0.56	0.456	

Data are expressed as n %

[a]Adjusted for correlation among women with multiple pregnancies, maternal race, obesity, infertility, gravidity, marital status using autoregressive correlation structure, using log binomial regression

[b]Any hypertensive complications include chronic hypertension, transient hypertension,mild preeclampsia, severe preeclampsia, and eclampsia

[c]Poisson distribution used instead of binomial distribution for estimating risk ratios

[d]Adjusted for obesity and gravidity

[e]Adjusted for obesity, gravidity, and maternal race

[f]Any diabetic complications include chronic diabetes mellitus, gestational diabetes, and abnormal glucose tolerance test

95% CI = 95% Confidence intervals

aRR = adjusted risk ratio

Table 5. Crude association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy outcomes for pregnancies of women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011 (n=2167)[a]

Pregnancy Outcomes	Total		≥ 35		35 - 39		≥ 40		cRR	95% CI		χ2	p-value	
Spontaneous Abortion														
No	1996	92.1	1627	93.7	369	85.6	1		referent					
Yes	171	7.9	109	6.3	62	14.4	1.96		1.58	2.44	31.22	< 0.001	*
Induced Abortion														
No	2132	98.4	1712	98.6	420	97.4	1		referent					
Yes	35	1.6	24	1.4	11	2.6	1.60		0.97	2.62	2.97	0.085		
Other types of abortions[b]														
No	2059	95.0	1659	95.6	400	92.8	1		referent					
Yes	108	5.0	77	4.4	31	7.2	1.48		1.08	2.01	5.54	0.019	*	
Other abnormal pregnancies not resulting in birth														
No	2111	97.4	1696	97.7	415	96.3	1		referent					
Yes	56	2.6	40	2.3	16	3.7	1.45		0.95	2.22	2.72	0.099		
Cesarean section among women delivering live births[c]														
No	1037	57.7	859	57.8	178	57.2	1		referent					
Yes	760	42.3	627	42.2	133	42.8	1.02		0.83	1.25	0.03	0.853		
Preterm birth among women with linked Georgia birth certificate data[d]														
No	1060	89.8	906	76.7	154	86.5	1		referent					
Yes	121	10.2	97	8.2	24	13.5	1.37		0.93	2.01	2.39	0.122		

Data are expressed as n %

[a]Not adjusted for correlation among women with multiple pregnancies

[b]Other types of abortions include illegal or unspecified abortions

[c]Among 1797 pregnancies that excludes pregnancies that did not result in live births (abortion and other abnormal

[d]Among 1181 pregnancies with linked Georgia birth certificate data

95% CI = 95% Confidence intervals

cRR = crude risk ratio

*Statistical significance at alpha=0.05

Table 6. Crude association of any hypertensive complications during pregnancy[a] and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Potential risk factors	Yes ases/ total (%	No cases/total (%)	cRR	95% CI		$\chi 2$	df	p-value	
Advanced maternal age (age ≥40)	51/178 (28.65)	74/1003 (17.35)	1.65	1.26	2.16	12.52	1	< 0.001	*
Obesity (BMI≥30)	105/306 (34.31)	109/790 (13.80)	2.48	1.97	3.14	59.08	1	< 0.001	*
Race						38.54	3	< 0.001	*
White	70/484 (14.46)	70/484 (14.46)	1	Referent					
Black	136/509 (26.72)	70/484 (14.46)	1.84	1.42	2.40	21.40	1	< 0.001	*
Asian	9/130 (6.92)	70/484 (14.46)	0.48	0.25	0.93	4.69	1	0.030	*
Other	10/58 (17.24)	70/484 (14.46)	1.19	0.65	2.18	0.33	1	0.569	
Unmarried	37/151 (24.50)	88/1030 (18.25)	1.34	0.99	1.83	3.34	1	0.068	
Education			-	-	-	3.80	3	0.284	
History of infertility	50/212 (23.58)	175/969 (18.06)	1.31	0.99	1.72	3.44	1	0.064	
Primigravida (No previous pregnancies)	71/268 (26.49)	154/913 (16.87)	1.57	1.23	2.01	12.45	1	< 0.001	*
History of transient hypertension[b,c]	3/16 (18.75)	151/897 (16.83)	1.11	0.40	3.12	-	-	0.742	
History of preeclampsia/eclampsia[b,c]	15/26 (61.54)	138/887 (15.56)	3.96	2.81	5.56	-	-	< 0.001	*
History of chronic diabetes mellitus	25/74 (33.78)	200/1107 (18.07)	1.87	1.33	2.63	11.11	1	< 0.001	*
History of gestational diabetes[b,c]	16/26 (61.54)	138/887 (15.56)	1.19	0.49	2.90	-	-	0.761	
Concurrent gestational diabetes	25/112 (22.32)	200/1069 (18.71)	1.19	0.83	1.72	0.86	1	0.354	
History of thyroid disorders	23/92 (25.00)	202/1089 (18.55)	1.35	0.93	1.96	2.29	1	0.130	
History of autoimmune disorders[c]	5/15 (33.33)	220/1166 (18.87)	1.77	0.86	3.65	-	-	0.180	
History of hypercoagulative disorders[c]	2/2 (100.00)	223/1179 (18.91	5.29	4.70	5.95	-	-	0.036	*

[a]Any hypertensive complications include chronic hypertension, transient hypertension, preeclampsia,
[b]Among multigravid women with previous pregnancies
[c]Fischer's exact test
cRR = crude risk ratio

Table 7. Crude association of transient hypertension and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Potential risk factors	Yes ases/ total (%	No cases/total (%)	cRR	95% CI		$\chi 2$	df	p-value
Advanced maternal age (age ≥40)	14/178 (5.06)	45/1003 (4.49)	1.13	0.56	2.26	0.11	1	0.737
Obesity (BMI≥30)	19/306 (6.21)	32/758 (4.05)	1.53	0.88	2.66	2.32	1	0.128
Race						1.79	3	0.617
White	26/484 (5.37)	26/484 (5.37)	1	Referent				
Black	22/509 (4.32)	26/484 (5.37)	0.80	0.46	1.40	0.59	1	0.442
Asian	3/130 (2.31)	26/484 (5.37)	0.43	0.13	1.40	1.97	1	0.160
Other	3/58 (5.17)	26/484 (5.37)	0.96	0.30	3.08	0.00	1	0.949
Unmarried	9/151 (5.96)	45/1030 (4.37)	1.36	0.68	2.73	0.76	1	0.382
Education	-	-	-	-	-	0.99	3	0.804
History of infertility	7/212 (3.30)	47/969 (4.85)	0.68	0.31	1.49	0.96	1	0.328
Primigravida (No previous pregnancies)	16/268 (5.97)	38/913 (4.16)	1.43	0.81	2.53	1.55	1	0.213
History of transient hypertension[a,b]	2/16 (12.50)	36/897 (4.01)	3.11	0.82	11.84	-	-	0.140
History of preeclampsia/eclampsia[a,b]	1/26 (3.85)	37/887 (4.17)	0.92	0.13	6.47	-	-	1.000
History of chronic diabetes mellitus[b]	2/74 (2.70)	52/1107 (4.70)	0.58	0.14	2.32	-	-	0.574
History of gestational diabetes[b]	1/23 (4.35)	53/1158 (4.58)	0.95	0.14	6.58	-	-	1.000
Concurrent gestational diabetes	7/112 (6.25)	47/1069 (4.40)	1.42	0.66	3.07	0.80	1	0.372
History of thyroid disorders[b]	6/92 (6.52)	48/1089 (4.41)	1.48	0.65	3.36	-	-	0.304
History of autoimmune disorders[b]	2/15 (13.33)	52/1166 (4.46)	2.99	0.80	11.16	-	-	0.147
History of hypercoagulative disorders[b]	1/2 (50.00)	53/1179 (4.50)	11.12	2.71	45.59	-	-	0.089

[a]Among multigravid women with previous pregnancies

[b]Fischer's exact test

cRR = crude risk ratio

Table 8. Crude association of preeclampsia/eclampsia and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Potential risk factors	Yes ases/ total (%	No cases/total (%)	cRR	95% CI		$\chi 2$	df	p-value	
Advanced maternal age (age ≥40)	11/178 (6.18)	52/1003 (5.18)	1.19	0.63	2.24	0.30	1	0.586	
Obesity (BMI≥30)	24/306 (7.84)	36/790 (4.56)	1.72	1.04	2.84	4.60	1	0.032	*
Race						11.08	3	0.011	*
White	19/484 (3.93)	19/484 (3.93)	1	Referent					
Black	39/509 (7.66)	19/484 (3.93)	1.95	1.14	3.33	6.02	1	0.014	*
Asian	2/130 (1.54)	19/484 (3.93)	0.39	0.09	1.66	1.62	1	0.204	
Other	3/58 (5.17)	19/484 (3.93)	1.32	0.40	4.32	0.21	1	0.649	
Unmarried	16/151 (10.60)	47/1030 (4.56)	2.10	1.34	3.30	9.49	1	0.002	*
Education	-	-	-	-	-	2.43	3	0.488	
History of infertility	15/212 (7.08)	48/969 (4.95)	1.43	0.82	2.50	1.55	1	0.213	
Primigravida (No previous pregnancies)	20/268 (7.46)	43/913 (4.71)	1.58	0.95	2.65	3.11	1	0.078	
History of chronic hypertension	23/131 (17.56)	40/1050 (3.81)	4.61	2.85	7.45	43.59	1	< 0.001	*
History of preeclampsia/eclampsia[a,b]	4/26 (15.38)	39/887 (4.40)	3.50	1.35	9.07	-	-	0.030	*
History of transient hypertension[a,b]	1/16 (6.25)	42/897 (4.68)	1.33	0.20	9.11	-	-	0.541	
History of chronic diabetes mellitus[b]	4/74 (5.41)	59/1129 (5.33)	1.01	0.38	2.72	-	-	1.000	
History of gestational diabetes[a,b]	2/20 (10.00)	41/893 (4.59)	2.18	0.57	8.39	-	-	0.242	
Concurrent gestational diabetes	6/112 (5.36)	57/1069 (5.33)	0.87	0.33	2.29	0.00	1	0.991	
History of autoimmune disorders[b]	2/15 (13.33)	61/1166 (5.23)	2.55	0.69	9.48	-	-	0.189	
History of hypercoagulative disorders[b]	1/2 (50.00)	62/1179 (5.26)	9.51	2.33	38.82	-	-	0.104	
History of thyroid disorders[b]	7/92 (7.61)	56/1089 (5.14)	1.48	0.69	3.15	-	-	0.329	

[a]Among multigravid women with previous pregnancies

[b]Fischer's exact test

cRR = crude risk ratio

*Statistical significance at alpha=0.05

Table 9. Crude association of diabetic complications during pregnancy[a] and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Potential risk factors	Yes cases/ total (%	No (or reference) cases/total (%)	cRR	95% CI		$\chi 2$	df	p-value	
Advanced maternal age (age≥40)	27/178 (15.17)	59/1003 (15.85)	0.96	0.66	1.39	0.05	1	0.817	
Obesity (BMI≥30)	75/306 (24.51)	98/790 (12.41)	1.98	1.51	2.59	24.31	1	< 0.001	*
Race						10.41	3	0.015	*
White	59/484 (12.19)	59/484 (12.19)	1	Referent					
Black	86/509 (16.90)	59/484 (12.19)	1.39	1.02	1.88	4.34	1	0.037	*
Asian	29/130 (22.31)	59/484 (12.19)	1.83	1.23	2.73	8.76	1	0.003	*
Other	12/58 (20.69)	59/484 (12.19)	1.70	0.97	2.96	3.46	1	0.063	
Unmarried	30/151 (19.87)	56/1030 (15.15)	1.31	0.92	1.86	2.21	1	0.137	
Education						9.03	3	0.029	*
Less than 8th grade or some high school (no dip	3/17 (17.65)	3/17 (17.65)	1	Referent					
High school grad, GED, or some college	30/155 (19.35)	3/17 (17.65)	1.10	0.37	3.22	0.03	1	0.866	
Associate:s or bachelor' degree	17/692 (16.91)	3/17 (17.65)	0.96	0.34	2.71	0.01	1	0.936	
Master's or doctorate degree	13/159 (7.98)	3/17 (17.65)	0.46	0.15	1.47	1.71	1	0.190	
History of infertility	38/212 (17.92)	148/969 (15.27)	1.17	0.85	1.62	0.92	1	0.337	
Primigravida (No previous pregnancies)	52/268 (19.40)	134/913 (14.68)	1.32	0.99	1.77	3.49	1	0.062	
History of chronic hypertension	39/131 (29.77)	147 /1050 (14.00)	2.13	1.57	2.88	21.83	1	< 0.001	*
History of transient hypertension[b,c]	2/16 (12.50)	132/897 (14.72)	0.85	0.23	3.14	-	-	1.000	
History of preeclampsia/eclampsia[b,c]	5/26 (19.23)	129/887 (14.54)	1.32	0.59	2.95	-	-	0.570	
History of gestational diabetes[b,c]	12/20 (60.00)	122/893 (13.66)	4.39	2.96	6.51	-	-	< 0.001	*
Concurrent transient hypertension	9/54 (16.67)	77/1127 (15.71)	1.06	0.58	1.96	0.04	1	0.850	
Concurrent preeclampsia/ eclampsia	10/63 (15.87)	76/1118 (15.74)	1.01	0.56	1.81	0.00	1	1	
History of autoimmune disorders[c]	2/15 (13.33)	84/1166 (15.78)	0.84	0.23	3.09	-	-	1	
History of hypercoagulative disorders[c]	2/2 (100.00)	86/1179 (15.78)	-	-	-	-	-	1	
History of thyroid disorders	16/92 (17.39)	70/1089 (15.61)	1.11	0.70	1.78	0.20	1	0.653	

[a]Any diabetic complications includes chronic diabetes and gestational diabetes
[b]Among multigravid women with previous pregnancies
[c]Fischer's exact test
cRR = crude risk ratio
*Statistical significance at alpha=0.05

Table 10. Crude association of gestational diabetes and potential risk factors among women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011, who had linked Georgia Birth Certificate data (n=1181)

Potential risk factors	Yes ases/ total (%	No (or reference) cases/total (%)	cRR	95% CI		$\chi 2$	df	p-value	
Advanced maternal age (age≥40)	17/178 (9.55)	95/1003 (9.47)	1.01	0.62	1.65	0.00	1	0.974	
Obesity (BMI≥30)	42/306 (13.73)	63/790 (7.97)	1.72	1.19	2.49	8.42	1	0.004	*
Race						15.86	3	0.001	*
White	38/484 (7.85)	38/484 (7.85)	1	Referent					
Black	42/509 (8.25)	38/484 (7.85)	1.05	0.69	1.60	0.05	1	0.817	
Asian	24/130 (18.46)	38/484 (7.85)	2.35	1.47	3.77	12.56	1	< 0.001	*
Other	8/58 (13.79)	38/484 (7.85)	1.76	0.86	3.58	2.41	1	0.121	
Unmarried	14/151 (9.27)	98/1030 (9.51)	0.97	0.57	1.66	0.01	1	0.924	
Education						10.54	3	0.015	*
Less than 8th grade or some high school (no dip	3/17 (17.65)	3/17 (17.65)	1	Referent					
High school grad, GED, or some college	23/155 (14.84)	3/17 (17.65)	0.84	0.28	2.51	0.10	1	0.756	
Associate:s or bachelor' degree	71/692 (10.26)	3/17 (17.65)	0.58	0.20	1.66	1.02	1	0.312	
Master's or doctorate degree	7/159 (4.40)	3/17 (17.65)	0.25	0.07	0.88	4.69	1	0.030	*
History of infertility	17/212 (8.02)	95/969 (9.80)	0.82	0.50	1.34	0.65	1	0.422	
Primigravida (No previous pregnancies)	37/268 (13.81)	75/913 (8.21)	1.68	1.16	2.43	7.55	1	0.006	*
History of chronic hypertension	16/131 (12.21)	96/1050 (9.14)	1.34	0.81	2.20	1.28	1	0.258	
History of transient hypertension[a,b]	1/16 (6.25)	74/897 (8.25)	0.76	0.11	5.12	-	-	1.000	
History of preeclampsia/eclampsia[a,b]	1/26 (3.85)	74/887 (8.34)	0.46	0.07	3.19	-	-	0.716	
History of gestational diabetes[a,b]	12/20 (60.00)	63/893 (7.05)	8.50	5.53	13.07	-	-	< 0.001	*
Concurrent transient hypertension	7/54 (12.96)	105/1127 (9.32)	1.39	0.68	2.84	0.80	1	0.372	
Concurrent preeclampsia/ eclampsia	6/63 (9.52)	106/1118 (9.48)	1.00	0.46	2.20	0.00	1	1	
History of autoimmune disorders[b]	1/15 (6.67)	111/1166 (9.52)	0.70	0.10	4.69	-	-	1	
History of hypercoagulative disorders[b]	0/2 (0.00)	112/1179 (9.50)	-	-	-	-	-	1	
History of thyroid disorders	12/92 (13.04)	100/1089 (9.18)	1.42	0.81	2.49	1.47	1	0.225	

[a]Among multigravid women with previous pregnancies
[b]Fischer's exact test
cRR = crude risk ratio
*Statistical significance at alpha=0.05

Table 11. Log Poisson regression model for estimating the log risk of any hypertensive complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data (n=1096)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value	
Intercept	-2.351	0.128	-2.603	-2.099			
Advanced age (≥40 years old)	0.460	0.131	0.202	0.717	8.93	0.003	*
Obesity (BMI≥30)	0.772	0.125	0.527	1.018	31.67	< 0.001	*
History of diabetes mellitus	0.388	0.169	0.057	0.718	3.79	0.052	
Primigravid	0.476	0.124	0.233	0.718	11.74	0.001	*
Maternal race (Black)	0.384	0.140	0.110	0.658	7.89	0.005	*
Maternal race (Asian)	-0.429	0.337	-1.089	0.232	2.15	0.143	
Maternal race (Other)	0.094	0.281	-0.456	0.645	0.10	0.747	

[a]Any hypertensive complications include chronic hypertension, transient hypertension, preeclampsia, or eclampsia
*Statistical significance at alpha=0.05

Table 12. Log Poisson regression model for estimating the log risk of any hypertensive complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of white maternal race (n=444)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value
Intercept	-2.525	0.186	-2.889	-2.161		
Advanced age (≥40 years old)	0.547	0.269	0.020	1.074	2.66	0.103
Obesity (BMI≥30)	1.250	0.217	0.824	1.676	18.99	< 0.001 *
History of diabetes mellitus	0.501	0.413	-0.309	1.310	0.95	0.329
Primigravid	0.321	0.239	-0.147	0.790	1.56	0.211

[a]Any hypertensive complications include chronic hypertension, transient hypertension, preeclampsia, or
*Statistical significance at alpha=0.05

Table 13. Log Poisson regression model for estimating the log risk of any hypertensive complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of black maternal race (n=481)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value	
Intercept	-1.799	0.134	-2.062	-1.536			
Advanced age (≥40 years old)	0.510	0.154	0.208	0.813	8.07	0.005	*
Obesity (BMI≥30)	0.530	0.147	0.242	0.818	12.08	0.001	*
History of diabetes mellitus	0.276	0.209	-0.134	0.686	1.35	0.246	
Primigravid	0.363	0.157	0.056	0.669	4.01	0.045	*

[a]Any hypertensive complications include chronic hypertension, transient hypertension, preeclampsia, or
*Statistical significance at alpha=0.05

Table 14. Log Binomial regression model for estimating the log risk of transient hypertension adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data (n=1096)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value
Intercept	-3.152	0.244	-3.631	-2.673		
Advanced age (≥40 years old)	0.075	0.378	-0.667	0.817	0.04	0.845
Obesity (BMI≥30)	0.524	0.308	-0.080	1.127	2.42	0.120
History of diabetes mellitus	-0.529	0.733	-1.965	0.907	0.80	0.371
Primigravid	0.461	0.305	-0.136	1.058	1.85	0.174
Maternal race (Black)	-0.259	0.309	-0.864	0.347	0.69	0.405
Maternal race (Asian)	-0.551	0.614	-1.755	0.653	1.09	0.296
Maternal race (Other)	0.056	0.590	-1.101	1.213	0.01	0.927
History of infertility	-0.400	0.415	-1.212	0.413	1.17	0.280
History of hypercoagulative disorde	2.459	0.748	0.992	3.925	0.92	0.339

Table 15. Log Poisson regression model for estimating the log risk of preeclampsia/eclampsia[a] adjusting for correlation among multiple pregnancies of the same women in the study population with Georgia Birth Certificate data (n=1181)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value	
Intercept	-3.444	0.227	-3.889	-2.999			
Advanced age (≥40 years old)	-0.188	0.315	-0.804	0.429	0.39	0.531	
History of chronic hypertension	1.426	0.264	0.909	1.943	13.84	< 0.001	*
Marital status (unmarried)	0.665	0.276	0.124	1.207	3.95	0.047	*
Maternal race (Black)	0.302	0.293	-0.272	0.877	1.1	0.294	
Maternal race (Asian)	-0.896	0.710	-2.287	0.495	2.92	0.088	
Maternal race (Other)	0.127	0.643	-1.133	1.387	0.04	0.850	

[a]Includes mild preeclampsia, severe preeclampsia, eclampsia, or preeclampsia/eclampia superimposed on chronic
*Statistical significance at alpha=0.05

Table 16. Log Poisson regression model for estimating the log risk of any diabetic complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with Georgia Birth Certificate data (n=1181)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value	
Intercept	-2.303	0.140	-2.577	-2.029			
Advanced age (≥40 years old)	-0.102	0.171	-0.437	0.232	0.40	0.526	
Obesity (BMI≥30)	0.832	0.168	0.502	1.162	1.01	0.316	
Maternal race (Black)	0.104	0.167	-0.223	0.432	0.40	0.529	
Maternal race (Asian)	0.798	0.207	0.393	1.203	9.44	0.002	*
Maternal race (Other)	0.439	0.243	-0.037	0.915	14.72	< 0.001	*

[a]Any diabetic complications includes chronic diabetes and gestational diabetes
*Statistical significance at alpha=0.05

Table 17. Log Poisson regression model for estimating the log risk of any diabetic complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of white maternal race (n=444)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value
Intercept	-2.379	0.169	-2.7102	-2.0478		
Advanced age (≥40 years old)	0.0001	0.0008	-0.0015	0.0017	0.01	0.914
Obesity (BMI≥30)	0.9702	0.2508	0.4786	1.4617	9.37	0.002 *

[a]Any diabetic complications includes chronic diabetes and gestational diabetes
*Statistical significance at alpha=0.05

Table 18. Log Poisson regression model for estimating the log risk of any diabetic complications[a] adjusting for correlation among multiple pregnancies of the same women in the study population with linked Georgia Birth Certificate data among mothers of Asian maternal race (n=116)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value
Intercept	-1.5369	0.1981	-1.9252	-1.1486		
Advanced age (≥40 years old)	0.3582	0.4608	-0.5449	1.2613	0.46	0.4982
Obesity (BMI≥30)	0.4382	0.6104	-0.7581	1.6346	0.34	0.5587

[a]Any diabetic complications includes chronic diabetes and gestational diabetes
*Statistical significance at alpha=0.05

Table 19. Log Poisson regression model for estimating the log risk of gestational diabetes adjusting for correlation among multiple pregnancies of the same women in the study population with Georgia Birth Certificate data (n=1096)

Parameter	Beta coefficient	Standard error	95% CI		Score test	p-value	
Intercept	-2.944	0.194	-3.324	-2.563			
Advanced age (≥40 years old)	-0.047	0.254	-0.545	0.450	0.04	0.849	
Obesity (BMI≥30)	0.803	0.208	0.396	1.210	11.52	0.001	*
Primigravida	0.627	0.190	0.254	1.000	8.04	0.005	*
Maternal race (Black)	-0.126	0.233	-0.583	0.331	0.29	0.593	
Maternal race (Asian)	1.103	0.255	0.603	1.602	10.31	0.001	*
Maternal race (Other)	0.565	0.356	-0.133	1.263	1.63	0.201	

*Statistical significance at alpha=0.05

Appendices

Appendix 1A. Characteristics of women by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB) for all women enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, including women without linked Georgia Birth Certificate data (n=1969)[a]

Characteristics	Total ≥ 35 (n = 1969)		35 - 39 (n = 1602)		≥ 40 (n = 367)		χ2	df	p-value	
Maternal age at FOB, mean (±SD)	37.4 (±2.3)		36.5 (±1.3)		41.3 (±1.5)					
Gestational age at FOB, mean (±SD)[b]	8.2 (±1.7)		8.1 (±1.6)		8.4 (±1.7)		-3.33	1967	0.001	*
Prepregnancy BMI, mean (±SD)[b]	27.5 (±6.3)		27.4 (±6.4)		27.7 (±6.2)		-0.72	1841	0.474	
Unknown, n %	127	6.4	103	6.4	24	6.5				
Obesity, n %										
Not Obese	1316	66.9	1076	67.2	240	65.4	0.56	1	0.456	
Obese	527	26.7	423	26.4	104	28.3				
Unknown	126	6.4	103	6.4	23	6.3				
Race, n %										
Black/African American	789	40.0	619	38.6	170	46.3	12.69	3	0.005	*
White	675	34.5	573	35.8	102	27.8				
Asian	208	10.6	176	11.0	32	8.7				
Other[d]	297	15.0	234	14.6	63	17.2				

[a]If women have multiple FOB visits, data from the earliest FOB visit for each women was included

[b]Pooled two sample t-test and t-test statistics

[c]Other includes other racial groups (n=30) consisting of American Indians, Alaskan Natives, Native Hawaiian and Pacific Islanders, multiracial, and unknown race (n=267)

*Statistical significance at alpha=0.05

Appendix 1B. Characteristics of women by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics/prenatal visit (FOB) for women enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, including multiple pregnancies by the same women during the study period, with or without linked Georgia Birth Certificate data (n=2167)[a]

Characteristics	Total ≥ 35 (n = 2167)		35 - 39 (n = 1736)		≥ 40 (n = 431)		χ2	df	p-value	
Maternal age at FOB, mean (±SD)	37.5 (±2.3)		36.6 (±1.4)		41.3 (±1.5)					
Gestational age at FOB, mean (±SD)[b]	8.2 (±1.7)		8.1 (±1.6)		8.4 (±1.7)		-3.06	2165	0.002	*
Prepregnancy BMI, mean (±SD)[b]	27.5 (±6.4)		27.4 (±6.4)		27.8 (±6.2)		-0.98	2032	0.328	
Unknown, n %	133	6.1	109	6.3	24	5.6				
Obesity, n %										
Not Obese	1447	66.8	1161	66.9	286	66.4	0.19	1	0.665	
Obese	587	27.1	466	26.8	121	28.1				
Unknown	133	6.1	109	6.3	24	5.6				
Race, n %										
Black/African American	857	39.5	658	37.9	199	46.2	14.11	3	0.003	*
White	753	34.7	630	36.3	123	28.5				
Asian	234	10.8	195	11.2	39	9.0				
Other[c]	323	14.9	253	14.6	70	16.2				

[a]χ2 tests and t-tests are not adjusted for correlation among women with multiple pregnancies

[b]Pooled two sample t-test and t-test statistics

[c]Other includes other racial groups (n=32) consisting of American Indian, Alaskan Native, Native Hawaiian, Pacific Islander, Multiracial, and unknown race (n=291)

*Statistical significance at alpha=0.05

Appendix 2A. Pre-existing conditions and past medical history by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of first obstetrics / prenatal visit (FOB) for both primigravid and multigravid women by pre-existing conditions for all women enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, including women without linked Georgia Birth Certificate data (n=1969)[a]

History	Total ≥ 35 (n = 1969)		35 - 39 (n = 1602)		≥ 40 (n = 367)		χ2	df	p-value	
Pre-existing hypertension										
No	1742	88.5	1437	89.7	305	83.1	12.73	1	< 0.001	*
Yes	227	11.5	165	10.3	62	16.9				
Pre-existing diabetes mellitus										
No	1850	94.0	1508	94.1	342	93.2	0.47	1	0.494	
Yes	119	6.0	94	5.9	25	6.8				
History of other diseases										
Depression										
No	1719	87.3	1413	88.2	306	83.4	6.27	1	0.012	*
Yes	250	12.7	189	11.8	61	16.6				
Seizure disorders[b]										
No	1960	99.5	1597	99.7	363	98.9	-	-	0.068	
Yes	9	0.5	5	0.3	4	1.1				
Thyroid disorders										
No	1817	92.3	1486	92.8	331	90.2	2.76	1	0.096	
Yes	152	7.7	116	7.2	36	9.8				
Autoimmune disorders[b]										
No	1946	98.8	1587	99.1	359	97.8	-	-	0.058	
Yes	23	1.2	15	0.9	8	2.2				
Hypercoagulative disorders[b]										
No	1967	99.9	1601	99.9	366	99.7	-	-	0.338	
Yes	2	0.1	1	0.1	1	0.3				
Deep vein thrombosis[b]										
No	1963	99.7	1596	99.6	367	100.0	-	-	0.601	
Yes	6	0.3	6	0.4	0	0.0				
Pulmonary embolism[b]										
No	1967	99.9	1601	99.9	366	99.7	-	-	0.338	
Yes	2	0.1	1	0.1	1	0.3				
Infertility[c]										
No	1598	81.2	1329	83.0	269	73.3	18.23	1	< 0.001	*
Yes	371	18.8	273	17.0	98	26.7				
Bacterial vaginosis										
No	1384	70.3	1141	71.2	243	66.2	3.59	1	0.058	
Yes	585	29.7	461	28.8	124	33.8				
Candidiasis										
No	1674	85.0	1363	85.1	311	84.7	0.04	1	0.869	
Yes	295	15.0	239	14.9	56	15.3				
Urinary tract infection										
No	1644	83.5	1260	78.7	384	104.6	0.28	1	0.595	
Yes	425	21.6	342	21.3	83	22.6				

Data are expressed as n %

[a]If women have multiple FOB visits, data from the earliest FOB visit for each women was included

[b]Fischer's exact test

[c]History of infertility includes ovary dysfunction, menopause, and history of infertility medication use

*Statistical significance at alpha=0.05

Appendix 2B. Pre-existing conditions and past medical history by maternal age groups (35 to less than 40, and equal to or greater than 40) at the time of their first obstetrics/prenatal visit (FOB) for both primigravid and multigravid women who were enrolled in Kaiser Permanente Georgia Health Plan from January 1, 2005 to August 31, 2011, including multiple pregnancies by the same women during the study period, with or without linked Georgia Birth Certificate data (n=2167)[a]

History	Total ≥ 35 (n = 2167)		35 - 39 (n = 1736)		≥ 40 (n = 431)		χ2	df	p-value	
Pre-existing hypertension										
No	1914	88.3	1558	89.7	356	82.6	17.11	1	< 0.001	*
Yes	253	11.7	178	10.3	75	17.4				
Pre-existing diabetes mellitus										
No	2032	93.8	1635	94.2	397	92.1	2.53	1	0.111	
Yes	135	6.2	101	5.8	34	7.9				
History of other diseases										
Depression										
No	1880	86.8	1519	87.5	361	83.8	4.21	1	0.040	*
Yes	287	13.2	217	12.5	70	16.2				
Seizure disorders[b]										
No	2156	99.5	1730	99.7	426	98.8	-	-	0.049	*
Yes	11	0.5	6	0.3	5	1.2				
Thyroid disorders										
No	1999	92.2	1609	92.7	390	90.5	2.33	1	0.127	
Yes	168	7.8	127	7.3	41	9.5				
Autoimmune disorders[b]										
No	2143	98.9	1720	99.1	423	98.1	-	-	0.119	
Yes	24	1.1	16	0.9	8	1.9				
Hypercoagulative disorders[b]										
No	2164	99.9	1734	99.9	430	99.8	-	-	0.486	
Yes	3	0.1	2	0.1	1	0.2				
Deep vein thrombosis[b]										
No	2160	99.7	1729	99.6	431	100.0	-	-	0.357	
Yes	7	0.3	7	0.4	0	0.0				
Pulmonary embolism[b]										
No	2164	99.9	1734	99.9	430	99.8	-	-	0.486	
Yes	3	0.1	2	0.1	1	0.2				
Infertility[c]										
No	1743	80.4	1429	82.3	314	72.9	19.64	1	< 0.001	*
Yes	424	19.6	307	17.7	117	27.1				
Bacterial vaginosis										
No	1502	69.3	1227	70.7	275	63.8	7.67	1	0.006	*
Yes	665	30.7	509	29.3	156	36.2				
Candidiasis										
No	1838	84.8	1478	85.1	360	83.5	0.70	1	0.404	
Yes	329	15.2	258	14.9	71	16.5				
Urinary tract infection										
No	1685	77.8	1352	77.9	333	77.3	0.08	1	0.782	
Yes	482	22.2	384	22.1	98	22.7				

Data are expressed as n %

[a]$\chi 2$ tests are not adjusted for correlation among women with multiple pregnancies

[b]Fischer's exact test

[c]History of infertility includes ovary dysfunction, menopause, and history of infertility medication use

*Statistical significance at alpha=0.05

Appendix 3. Crude association of maternal age (maternal age groups 35 to less than 40, and equal to or greater than 40) and pregnancy complications for all pregnancies, including multiple pregnancies for women enrolled in Kaiser Permanente Georgia Health Plan, January 1, 2005 to August 31, 2011 (n=2167)[a]

Outcome	Total ≥ 35 (n = 2167)		35 - 39 (n = 1736)		≥ 40 (n = 431)		cRR	95% CI		χ2	df	p-value	
Hypertensive complications													
Any hypertensive complications[b]													
No	1770	81.7	1438	82.8	332	77.0	1	referent					
Yes	397	18.3	298	17.2	99	23.0	1.33	1.09	1.62	7.77	1	0.005	*
Chronic hypertension													
No	1914	88.3	1558	89.7	356	82.6	1	referent					
Yes	253	11.7	178	10.3	75	17.4	1.59	1.29	1.97	17.11	1	< 0.001	*
Transient hypertension													
No	2084	96.2	1666	96.0	418	97.0	1	referent					
Yes	83	3.8	70	4.0	13	3.0	0.78	0.47	1.30	0.97	1	0.325	
Preeclampsia or eclampsia													
No	2070	95.5	1660	95.6	410	95.1	1	referent					
Yes	97	4.5	76	4.4	21	4.9	1.09	0.74	1.61	0.20	1	0.657	
Mild pre-clampsia													
No	2105	97.1	1690	97.4	415	96.3	1	referent					
Yes	62	2.9	46	2.6	16	3.7	1.31	0.85	2.01	1.40	1	0.236	
Severe pre-clampsia/eclampsia													
No	2132	98.4	1706	98.3	426	98.8	1	referent					
Yes	35	1.6	30	1.7	5	1.2	0.72	0.32	1.62	0.70	1	0.402	
Diabetic complications													
Any diabetic complications[c]													
No	1826	84.3	1472	84.8	354	82.1	1	referent					
Yes	341	15.7	264	15.2	77	17.9	1.16	0.94	1.45	1.84	1	0.175	
Chronic diabetes mellitus													
No	2032	93.8	1635	94.2	397	92.1	1	referent					
Yes	135	6.2	101	5.8	34	7.9	1.29	0.95	1.75	2.53	1	0.111	
Gestational diabetes													
No	1961	90.5	1573	90.6	388	90.0	1	referent					
Yes	206	9.5	163	9.4	43	10.0	1.06	0.80	1.40	0.14	1	0.710	
Other pregnancy complications													
Anemia													
No	1848	85.3	1482	85.4	366	84.9	1	referent					
Yes	319	14.7	254	14.6	65	15.1	1.03	0.81	1.30	0.06	1	0.814	
Thyroid disorders complicating pregnancy													
No	2024	93.4	1623	93.5	401	93.0	1	referent					
Yes	143	6.6	113	6.5	30	7.0	1.06	0.76	1.47	0.11	1	0.736	
Bacterial vaginosis													
No	2034	93.9	1638	94.4	396	91.9	1	referent					
Yes	133	6.1	98	5.7	35	8.1	1.35	1.00	1.82	3.67	1	0.055	
Candidiasis													
No	2071	95.6	1661	95.7	410	95.1	1	referent					
Yes	96	4.4	75	4.3	21	4.9	1.11	0.75	1.63	0.25	1	0.618	
Urinary tract infections													
No	2026	93.5	1625	93.6	401	93.0	1	referent					
Yes	141	6.5	111	6.4	30	7.0	1.08	0.77	1.49	0.18	1	0.670	

Data are expressed as n %

[a]Not adjusted for correlation among women with multiple pregnancies

[b]Any hypertensive complications include chronic hypertension, transient hypertension,mild preeclampsia, severe

[c]Any diabetic complications include chronic diabetes mellitus, gestational diabetes, and abnormal glucose tolerance test result during pregnancy

95% CI = 95% Confidence intervals

cRR = crude risk ratio

*Statistical significance at alpha=0.05