Preventing Postpartum Preeclampsia with Low-Dose Aspirin: A Randomized Controlled Trial

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PREVENTING POSTPARTUM PREECLAMPSIA WITH LOW-DOSE ASPIRIN: A
RANDOMIZED CONTROLLED TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
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ABSTRACT

Preeclampsia, defined as new or worsening hypertension along with new onset proteinuria and/or end organ damage throughout pregnancy, is one of the leading causes of perinatal and maternal morbidity and mortality. Antepartum preeclampsia has been extensively studied, and prophylaxis with 81mg aspirin starting between 12- and 16-weeks’ gestation is the current standard for prevention. However, little is known about the prevention of new onset postpartum preeclampsia, which can present up to 6 weeks postpartum. In this study, we will evaluate the efficacy of aspirin in preventing the incidence of new onset postpartum preeclampsia. Using a randomized controlled trial, we will determine whether continuing low-dose aspirin use for 6 weeks postpartum is an effective intervention in preventing new onset postpartum preeclampsia in patients with risk factors. These results will provide evidence in favor of a cost-effective treatment regimen that could prevent new onset postpartum preeclampsia and help reduce morbidity and mortality.
CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 Preeclampsia

Preeclampsia is one of the leading causes of perinatal and maternal morbidity and mortality.\textsuperscript{1} It affects 3-8\% of pregnancies in the United States (U.S.), and is the second leading cause of maternal death worldwide.\textsuperscript{2} Preeclampsia is defined as a hypertensive disorder in pregnancy that is characterized by new or worsening hypertension with a systolic blood pressure greater than 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg, along with new onset proteinuria and/or end organ damage occurring after 20 weeks’ gestation.\textsuperscript{3,4} It can lead to adverse maternal and neonatal complications such as eclampsia, HELLP syndrome, stroke, liver rupture, preterm birth, intrauterine growth restriction (IUGR), miscarriage, or stillbirth.\textsuperscript{2,5} Preeclampsia has also been associated with long term maternal consequences, including increased risk of future cardiovascular events, and cerebrovascular and metabolic disease.\textsuperscript{2} The incidence of preeclampsia has been rising in the U.S. over the last 3 decades leading to a substantial financial burden on the U.S. healthcare system.\textsuperscript{1}

1.1.2 New Onset Postpartum Preeclampsia

Many of the studies done on preeclampsia focus primarily on antepartum preeclampsia, which includes preterm preeclampsia presenting before 37 weeks’ gestation and term preeclampsia present at or after 37 weeks’ gestation. Less is known about postpartum preeclampsia, presenting after delivery and before 6 weeks postpartum, and the mechanisms underlying its development.\textsuperscript{6} Currently, the evidence regarding new onset postpartum preeclampsia is limited; there is no clear data on the pathophysiology,
clinical course, management and prevention of the disease. Since delivery of the placenta is believed to be the cure for antepartum preeclampsia, some researchers hypothesize that postpartum preeclampsia may be an entirely different disorder. However, recent evidence suggests that the two disorders likely stem from the same etiology.

Recent studies have compared the risk factors for antepartum and postpartum preeclampsia, and determined that there was no significant difference in risk factors between the two. One study determined that the placentas of antepartum and postpartum preeclampsia had elevated immune cells, such as CD45+ T cells, indicating that there is likely a prenatal initiation of the pathophysiology. Another study found no difference in the placental findings of late-onset antepartum preeclampsia and postpartum preeclampsia, suggesting the two share a common pathophysiology. Goel et al (2015) found that sFlt1 and PIGF, two angiogenic factors that are central to the pathogenesis of preeclampsia, followed the same pattern in antepartum and postpartum preeclampsia—higher sFlt1, lower PIGF, and higher sFlt1/PIGF ratio. These results indicate that the pathogenesis of postpartum preeclampsia is similar to that of antepartum preeclampsia.

1.1.3 The Placenta and Preeclampsia

Antepartum preeclampsia and its clinical symptoms subside after delivery, which has led to the hypothesis that the placenta is central to the pathophysiology of the disease. In preeclampsia, there is a “two step” process that leads to abnormal placentation. In the first trimester there is abnormal invasion of trophoblasts and insufficient uterine spinal arterial remodeling that leads to reduced uteroplacental perfusion. The decreased perfusion can eventually lead to ischemia as well as an abnormal maternal vascular response. Proinflammatory cytokines, angiogenic factors
such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), and anti-angiogenic factors such soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), are released from the poorly perfused placenta into the maternal circulation, impairing maternal systemic vasculature function which ultimately leads to the clinical manifestations seen in preeclampsia.\textsuperscript{8,11}

In preeclampsia, an imbalance of these factors occurs favoring anti-angiogenic factors which causes maternal vasoconstriction and ultimately increased maternal blood pressure. This increase in maternal blood pressure is necessary in order to adequately perfuse the placenta.\textsuperscript{8} The release of pro-inflammatory cytokines activates an inflammatory response that triggers cyclooxygenase (COX) resulting in increased thromboxane A2 (TxA2) levels and decreased prostacyclin levels (PGI2).\textsuperscript{12} TxA2 is associated with increased platelet aggregation and vasoconstriction, and without PGI2 to counteract the higher levels of TxA2, there is more maternal vasoconstriction leading to the clinical symptoms seen during preeclampsia.\textsuperscript{12}

1.1.4 The Role of Aspirin in Pregnancy

Aspirin irreversibly inhibits COX and is selective for COX-1 at lower doses and COX-2 at higher doses.\textsuperscript{12,14} COX-1 regulates levels of TxA2 and PGI2; inhibition of COX-1 by aspirin increases levels of PGI2 and decreases levels of TxA2. This leads to systemic vasodilation that counteracts the vasoconstriction seen in preeclampsia.\textsuperscript{15} Aspirin’s inhibition of COX-1 also inhibits sFlt-1 overexpression, which counteracts the mechanism of preeclampsia.\textsuperscript{2} Currently, the American College of Obstetricians and Gynecologists (ACOG) recommends initiating 81mg aspirin starting $\leq$16 weeks’ gestation for pregnant women at an increased risk for the development of preeclampsia.\textsuperscript{16}
The United States Preventative Services Task Force (USPSTF) also recommends the use of 81mg aspirin in pregnancy for any pregnant woman who is at an increased risk of developing preeclampsia.\textsuperscript{17}

Aspirin use in pregnancy has been extensively studied and determined to be safe. Both ACOG and the USPSTF have conducted meta analyses that determined the use of low-dose aspirin during pregnancy is safe and associated with a low likelihood of serious maternal or fetal complications, such as placental abruption, postpartum hemorrhage, congenital anomalies, and premature closure of ductus arteriosus.\textsuperscript{16,18} The use of low-dose aspirin during the first trimester has not been found to be teratogenic,\textsuperscript{15} and is also not considered a contraindication for neuraxial blockade during labor.\textsuperscript{19}

1.2 Statement of the Problem

A study published in 2012 found that the prevalence of new onset postpartum preeclampsia was 0.3\%-27.5\%, with the large range likely because many women do not have their blood pressure measured until their 6 week postpartum follow up, and the prevalence is likely to vary in different populations.\textsuperscript{20} 50\% of eclampsia cases develop after delivery, and 26\% of seizures develop more than 48 hours after birth.\textsuperscript{21} Postpartum preeclampsia represents a significant burden on maternal morbidity. Women who develop new onset postpartum preeclampsia have increased odds for hospital readmission, requiring magnesium sulfate during hospitalization for seizure prophylaxis, and being discharged with a prescription for antihypertensive medication.\textsuperscript{7} There is also a significantly higher risk during readmission for severe cerebrovascular complications, such as eclampsia and stroke, in women without an antepartum and/or delivery
hypertensive diagnosis.\textsuperscript{22,23} Despite these numbers, less attention has been given to postpartum preeclampsia and its prevention.

Currently, there is very limited evidence on new onset postpartum preeclampsia, with the majority of the literature about antepartum preeclampsia. Specifically, there have been no studies examining the prevention of postpartum preeclampsia. If the underlying disease process of postpartum preeclampsia shares a common pathophysiology with antepartum preeclampsia, then the use of low-dose aspirin during the postpartum period may prevent the development of new onset postpartum preeclampsia. The current ACOG and USPSTF guidelines recommend terminating aspirin at delivery; however, more studies are needed to determine whether this is sufficient enough to prevent postpartum preeclampsia, or whether low-dose aspirin should be continued beyond delivery since postpartum preeclampsia can develop up to 6 weeks postpartum.

1.3 Goals and Objectives

Our proposed study aims to evaluate the effects of 81mg aspirin use during the postpartum period. More specifically, we will examine whether 81mg aspirin started at up to 2 days postpartum and continued until 6 weeks postpartum will be an effective intervention in reducing the incidence of new onset postpartum preeclampsia as compared with controls who stop their aspirin at admission for delivery. The results of this study will provide evidence for the efficacy of low-dose aspirin in the prevention of new onset postpartum preeclampsia, which will ultimately help reduce maternal morbidity and mortality that can occur as a consequence of the disease.

1.4 Hypothesis
Among women who are at an increased risk for developing preeclampsia, the use of 81mg aspirin once daily during the postpartum period starting by 2 days postpartum continued until 6 weeks postpartum will have a statistically significant difference in the incidence of new onset postpartum preeclampsia compared to placebo.

1.5 Definitions

**Women at an increased risk for developing preeclampsia:** must have at least 1 high risk factor or 2 or more moderate risk factors

**High risk factors:** history of preeclampsia (especially when accompanied by an adverse outcome); multifetal gestation; chronic hypertension; type I or II diabetes; renal disease; or autoimmune disease such as systemic lupus erythematosus or anti-phospholipid syndrome\(^1^6\)

**Moderate risk factors:** nulliparity, obesity (BMI > 30), family history of preeclampsia (mother or sister), sociodemographic characteristics (African American race, low socioeconomic status), age ≥ 35 years, and personal history factors (low birthweight or small for gestational age, previous adverse pregnancy outcome, >10 year pregnancy interval)\(^1^6\)
References


CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

We conducted a literature search using the PubMed, Cochrane, Scopus, MEDLINE, and Ovid databases between July 2020 and May 2021. The following MeSH terms were included: [postpartum preeclampsia], [preeclampsia], [postpartum hypertension], [postpartum period], [pregnancy induced hypertension], [preterm preeclampsia], [gestational hypertension], [aspirin], [aspirin safety], and [acetylsalicylic acid]. Additional relevant studies were selected from the reference lists of the studies selected. Only articles published in the English language were selected. We included systematic reviews and meta-analyses, randomized controlled trials (RCT), case-control, and cohort studies. In this review, we will analyze and identify the strengths and limitations of these studies, and how our study will attempt to fill in the gaps in the literature.

2.2 Preeclampsia

2.2.1 Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy are considered a major health issue for women and infants in the United States (U.S.). These disorders, which include chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and chronic hypertension with superimposed preeclampsia, are some of the leading causes of maternal and fetal morbidity and mortality. Preeclampsia, both alone and superimposed, constitutes the majority of significant complications associated with hypertensive disorders of pregnancy. In the U.S., 18% of maternal deaths can be directly attributed to preeclampsia; worldwide, preeclampsia is the second leading cause of maternal death.
In 2012, the total cost burden of preeclampsia was $1.15 billion for infants and $1.03 billion for mothers. In 2015, one study showed that compared with uncomplicated full term pregnancies, preeclampsia was associated with total estimated mean incremental increased cost of $28,603 more due to neonatal morbidity related to prematurity.

2.2.2 Antepartum and Postpartum Preeclampsia

The American College of Obstetricians and Gynecologists (ACOG) defines preeclampsia as new or worsening hypertension after 20 weeks’ gestation with evidence of proteinuria and/or end organ damage, and it may lead to the development of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome or eclampsia (new onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions). While the pathophysiology of preeclampsia is not fully elucidated, it is generally hypothesized as being due to abnormal placentation that occurs in a “two-step process”. In a normal pregnancy, fetal cytotrophoblasts migrate into the maternal uterus, penetrate and remodel the spiral arteries of the endometrium which supply blood to the placenta. The cytotrophoblasts are transformed from an epithelial to an endothelial phenotype, a process called pseudovasculogensis. This upregulates the expression of molecules that are necessary for uterine invasion, such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF).

In the “first step” of preeclampsia, there is inadequate invasion of the fetal cytotrophoblasts around 12-16 weeks’ gestation, leading to poor placental perfusion and ischemia. This relative ischemia and decreased perfusion causes the release of damaging factors, such as oxidized lipids and antiangiogenic factors, into the maternal bloodstream. This results in the “second step” where a systemic maternal inflammatory
response is launched. During this inflammatory process, there is an inadequate release of pro-angiogenic factors, such as VEGF and PlGF, coupled with upregulated release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), from the placenta. This angiogenic imbalance (increased sFlt-1 and sEng, decreased VEGF and PlGF) leads to an immune-mediated exaggerated inflammatory response and endothelial cell dysfunction resulting in increased systemic vascular resistance, enhanced platelet aggregation, and abnormal activation of the coagulation system. This cascade contributes to the clinical symptoms seen in preeclampsia, such as hypertension, proteinuria, and symptoms of end organ damage.

Increased sFlt-1 and sEng are the source for maternal vasoconstriction and hypertension, which is believed to occur in an effort to increase placental perfusion. Additionally, the inflammatory response that occurs activates cyclooxygenase (COX), which increases thromboxane A2 (TxA2) levels and reduces endothelial cell prostacyclin levels (PIG2). TxA2 increases platelet aggregation and vasoconstriction, and PIG2 counteracts these effects. This imbalance further contributes to the inflammatory response and clinical spectrum of disease. Pre-existing hypertension, diabetes, and other inflammatory conditions, such as lupus, as well as multifetal gestation, are thought to precipitate the maternal systemic inflammatory response seen in preeclampsia.

The majority of the current literature about preeclampsia focuses on antepartum preeclampsia; there is very little literature regarding postpartum preeclampsia, which can occur up to 6 weeks postpartum. Women can develop new onset postpartum preeclampsia with a previously normotensive pregnancy, or can have persistent or exacerbated postpartum hypertension and/or preeclampsia after a pregnancy complicated
by preeclampsia or another hypertensive pregnancy diagnosis.\textsuperscript{7} Patients who have been readmitted with postpartum hypertension or preeclampsia have generally not been reported in studies that focused on preeclampsia as a primary outcome, further contributing to the lack of data in the current literature. Recent studies have found that postpartum and antepartum preeclampsia may share a similar etiology and pathophysiology, as well as similar risk factors. The data in the literature has been retrospective in nature\textsuperscript{13-18}; no RCTs or prospective studies have been conducted, and specifically none have looked at prevention of postpartum preeclampsia.

In a 2015 retrospective study published by Goel et al, the authors found that women who developed de novo postpartum hypertension had similar clinical risk factors to women who developed persistent postpartum hypertension, and these strongly resembled risk factors for preeclampsia.\textsuperscript{18} Women with de novo postpartum hypertension also had significantly higher antepartum sFlt1 levels compared to women who remained normotensive postpartum (median\textsuperscript{25\textth{-75\textth %ile}}: 10189pg/ml [5655,16650] vs 7721 pg/ml [5088,12199] p=0.004) and significantly higher antepartum sFlt1/PIGF ratios (median\textsuperscript{25\textth{-75\textth %ile}}: 52.1 [22.0, 84.6] vs 33.1 [14.1, 65.9] p=0.002).\textsuperscript{18} Similar results were seen in women with a hypertensive pregnancy diagnosis with persistent postpartum hypertension compared to those who remained normotensive postpartum (sFlt1 median\textsuperscript{25\textth{-75\textth %ile}}: 13067pg/ml [8660,22816] vs 11708pg/ml [7429,16417] p=0.02; sFlt1/PIGF median\textsuperscript{25\textth{-75\textth %ile}}: 93.9 [47.3,199.3] vs 57.2 [26.0,128.8] p < 0.001).\textsuperscript{18} These results showed an identical pattern of circulating antepartum angiogenic factors in postpartum preeclampsia as those seen in antepartum preeclampsia (higher sFlt1 and sFlt1/PIGF)\textsuperscript{8}, and for the first time suggested a similar pathophysiology between the two.
The study, however, was limited to women undergoing c-section only and may have introduced bias while also limiting the generalizability of the results.

In a retrospective study published by Ditisheim et al (2019) comparing the placentas of women with early-onset preeclampsia, late-onset preeclampsia, postpartum preeclampsia, and normal controls, the authors found no difference in the placental pathologies of postpartum preeclampsia and late-onset preeclampsia, which included immune-inflammatory lesions and maternal vascular malperfusion findings (all p>0.05). These results suggested that both entities share a common pathophysiology, similar to the results from Goel et al’s study. Some limitations in the study were the small sample size (n=129), the pathologist was not blinded to the clinical diagnosis which may have introduced bias, and the inclusion of chronic hypertension and diabetes mellitus which may have acted as potential confounders on placental morphology. More recently, a retrospective study published in 2020 found that there was no significant difference in clinical risk factors between women with new onset postpartum preeclampsia, women with antepartum preeclampsia who developed postpartum preeclampsia, and women with antepartum preeclampsia who did not develop postpartum preeclampsia. The evidence from these studies showing similar risk factors and antiangiogenic factor profiles supports the hypothesis that antepartum and postpartum preeclampsia have a similar pathogenesis, and postpartum preeclampsia may even be a form of subclinical or late-onset (after delivery) preeclampsia. Therefore, investigations into the prevention of postpartum preeclampsia may benefit from examining whether aspirin, the current standard of care for prevention of preterm preeclampsia, may have the same effect on the incidence of postpartum preeclampsia.
2.2.3 Sequelae

Cardiovascular disease (CVD) is the number one cause of mortality in women in the U.S.\textsuperscript{19} Classic CVD risk factors are associated with preeclampsia; because of this, women with a history of preeclampsia have an elevated risk of CVD later in life. In a systematic review and meta-analysis published in 2013, Brown et al found that women with a history of preeclampsia were at more than twofold increased odds of developing CVD later in life (OR=2.28, 95% CI 1.87-2.77).\textsuperscript{20} The 14 studies included had a high degree of heterogeneity ($I^2=78.9\%$, $p<0.001$), but there was no evidence of bias ($p=0.166$).\textsuperscript{20} The high heterogeneity was partially explained by the stronger effect of fatal outcomes compared to diagnosed outcomes. The odds of a fatal outcome (OR=2.89, 95% CI 1.71-4.89) were greater than the odds of a diagnosis (OR=2.01, 95% CI 1.68-2.41) with a higher degree of heterogeneity for fatal outcomes compared to diagnosis ($I^2=83\%$ vs 64.9\% respectively).\textsuperscript{20}

In the same meta-analysis, women with a history of preeclampsia were found to be at increased odds of a cerebrovascular event (OR=1.77, 95% CI 1.43-2.21), and there was no strong evidence of bias ($p=0.209$) or heterogeneity ($I^2=48.2\%$, $p=0.072$).\textsuperscript{20} Women with a history of preeclampsia were also at increased risk of developing hypertension (RR=3.13, 95% CI 2.51-3.89), with a high degree of heterogeneity between studies ($I^2=88.6\%$, $p<0.001$) but no evidence of publication bias ($p=0.854$). The substantial heterogeneity may have been due to differences in study quality. Higher quality studies had a slightly higher RR compared to lower quality studies (RR=3.18, 95% CI 2.07-4.88 vs RR=3.11, 95% CI 2.42-3.99) as well as lower heterogeneity in the higher quality studies compared to the lower quality studies ($I^2=50.2\%$ vs 91.5\%).\textsuperscript{20}
Heterogeneity may also be due to the fact that all types of cardiovascular and cerebrovascular events were combined; therefore, they could not investigate whether certain types of events were more strongly associated with preeclampsia. These results were similar to previously published systematic reviews and meta-analyses.\textsuperscript{21,22}

Women who develop postpartum hypertension or preeclampsia have the highest risk for severe maternal morbidity due to decreased surveillance during the puerperium period and lack of data regarding preventive therapies and interventions. In a retrospective cohort study conducted by Al-Safi et al (2011), the authors found that for patients readmitted to the hospital between 2 days and 6 weeks postpartum with the diagnosis of postpartum preeclampsia, the overall rate of eclampsia was 14.5\% (n=22, 95\% CI 9.8-20.9).\textsuperscript{23} Eclampsia was also more common in patients who had no antecedent diagnosis of hypertension in pregnancy (n=17, 77.3\%, 95\% CI 56.6-89.9).\textsuperscript{23} Some limitations from this study include the retrospective nature of the study which may not have included all patients with postpartum preeclampsia, as mild forms of the disease may have resolved without patients seeking care. Missing data from records identified may have also led to less participants being included in the results.

In a cohort study published in 2019, Wen et al sought to analyze risk factors and outcomes for women readmitted during the first 60 days postpartum for a hypertensive indication. The rate for readmission within 60 days for postpartum hypertensive diseases of pregnancy or hypertension among women without any hypertensive diagnosis in pregnancy (gestational hypertension, preeclampsia, or eclampsia) was 0.15\% compared to 1.13\% in women with hypertensive diseases of pregnancy or chronic hypertension.\textsuperscript{24} In a secondary analysis evaluating maternal morbidity, the authors found that the overall
risk for morbidity was higher in women without a previous hypertensive pregnancy diagnosis compared to women with a previous hypertensive pregnancy diagnosis (12.1% vs 6.9%, p<0.01).24 Women without a previous hypertensive pregnancy diagnosis were also at a significantly higher risk during readmission for eclampsia (9.1% vs 2.3%, p<0.01) and stroke (1.2% vs 0.5%, p<0.01).24 The limitations of this study were mainly due to the inherent shortcomings of administrative data, such as not being able to assess blood pressure readings during hospitalization or under-coding of hypertensive diagnoses of pregnancy. Another limitation was that patients could not be tracked across calendar years; therefore, analyses were limited to January-October of each year.

Postpartum hypertension has been found to increase the risk of cerebral hemorrhage.18 Despite evidence showing that persistent and de novo hypertension occurring within 6 weeks postpartum increases the risk for severe cerebrovascular complications25, blood pressure monitoring is commonly left out of the follow-up during the puerperium. By underestimating its clinical importance, many women with postpartum hypertension or preeclampsia may develop severe complications like stroke and future CVD. Therefore, studies to examine the prevention of postpartum preeclampsia, such as our proposed study, are justified in order to decrease the burden of maternal morbidity associated with the disease.

2.3 Aspirin and Preeclampsia

2.3.1 Aspirin Use and Risk of Preeclampsia

Since the publication of landmark trials by Sibai et al in 199326 and the CLASP trial in 199427, there has been much interest in the use of aspirin for the prevention of preeclampsia. In a systematic review for the USPSTF, Henderson et al (2014) looked at
placebo-controlled RCTs published prior to 2013 to determine whether the use of aspirin reduced the incidence of preeclampsia in women at an increased risk, as well as adverse maternal and fetal outcomes. In the pooled estimate for preeclampsia incidence, the authors found a 24% reduction (RR=0.76, 95% CI 0.62-0.95) with moderate heterogeneity across studies ($I^2=40.5\%, \ p=0.064$). There was, however, evidence of small sample bias (Peter’s $p=0.03$), as a significant reduction in the incidence of preeclampsia was not seen in the 2 largest trials although they both estimated about a 10% reduction.\textsuperscript{27,28} When stratifying by aspirin dosage, the estimated risk reduction was greater in studies using aspirin >75 mg (RR=0.58, 95% CI 0.36-0.95) compared to ≤75 mg (RR=0.85, 95% CI 0.68-1.05).\textsuperscript{9} This may have also been confounded by small study effects, as the two largest studies used 60 mg aspirin.\textsuperscript{27,28} Henderson et al (2014) also found a significantly reduced risk of adverse perinatal outcomes, including perinatal mortality, intrauterine growth restriction (IUGR), low birthweight, and preterm birth with low-dose aspirin use.\textsuperscript{9}

The pooled results of this analysis may have overestimated the benefit of low-dose aspirin given the evidence of small study effects. However, the consistency in the effect size in the 2 larger trials revealed evidence supporting at least a 10% reduction in the incidence of preeclampsia in women at an increased risk.\textsuperscript{9} This evidence supported a causal pathway to observed direct health outcomes for which the USPSTF used to update its recommendations on the use of low-dose aspirin for the prevention of preeclampsia. Another limitation was that some of the benefits evaluated were rare events, indicating that there may have been insufficient power to detect beneficial events. Lastly, few of the studies included were conducted in the U.S.; however, the authors only included studies
from the “high development index” in order to minimize dissimilarities that would limit applicability of results.

More recently, a large multicenter, double-blind placebo-controlled RCT conducted by Rolnik et al (2017) including 1,776 women with singleton pregnancies who were considered high risk for preeclampsia found that 150mg aspirin initiated between 11-14 weeks’ gestation and continued until 36 weeks’ gestation was associated with a significantly lower incidence of preterm preeclampsia (<37 weeks) than placebo (1.6% versus 4.3% respectively, aOR=0.38, 95% CI 0.20-0.74, p=0.004). There was high compliance in this study (79.9%), which may have contributed to the beneficial effect seen. Aspirin did not reduce the incidence of term preeclampsia (≥37 weeks) (6.6% versus 7.2%, aOR=0.95, 99% CI 0.57-1.57), however, the trial was not powered for this secondary outcome. One explanation is that aspirin delays the onset of preeclampsia signs/symptoms and shifts the gestational age at delivery to the right so that women present with term versus preterm deliveries, and ultimately improves neonatal outcomes. This theory explains why there was a nonsignificant reduction seen with term preeclampsia. Rolnik et al’s (2017) study was the biggest prospective, placebo-controlled RCT on the prophylactic use of aspirin in women at an increased risk of preeclampsia, and established the efficacy of aspirin in the prevention of preterm preeclampsia.

2.3.2 Aspirin and Postpartum Preeclampsia

With recent evidence supporting the hypothesis that the pathogenesis of postpartum preeclampsia is similar to that of antepartum preeclampsia, is it reasonable to consider extending low-dose aspirin prophylaxis beyond delivery up until 6 weeks postpartum. Aspirin’s beneficial role in preeclampsia has been hypothesized to be
due to its irreversible inhibition of COX-1\(^3\) at low doses which results in decreased TxA2 levels counteracting the elevated TxA2 seen in preeclampsia, and thereby decreasing vasoconstriction and platelet aggregation.\(^{11}\) By inhibiting COX-1, aspirin also inhibits the overexpression of sFlt1 levels which are seen in preeclampsia\(^{31}\), resulting in increased VEGF and promotes angiogenesis.\(^{10}\) Aspirin has also been found to reduce the maternal endothelial cell dysfunction seen in preeclampsia by reducing circulating levels of pro-inflammatory markers.\(^{10}\) With the results from Goel et al (2015) showing higher sFlt1 and sFlt1/PlGF levels in postpartum preeclampsia similar to antepartum preeclampsia\(^{18}\), we hypothesize that extending low-dose aspirin prophylaxis beyond delivery up until 6 weeks postpartum will allow for continued action in the prevention of preeclampsia.

### 2.3.3 Aspirin Safety in Pregnancy and the Postpartum Period

Although aspirin is widely regarded as a safe medication, it is associated with some adverse effects that vary in type and severity with the dosage and duration of use as well as underlying patient risk factors. Aspirin can cause mucosal damage in the gastrointestinal (GI) tract which can lead to erosions, ulcers, and bleeding;\(^{32}\) therefore any history of GI ulcers and/or bleeding is usually contraindicated. A major concern with aspirin use, however, is the increased risk of non-GI bleeding, such as intracranial bleeds and hemorrhagic stroke. In a systematic review for the USPSTF examining bleeding risks with aspirin use for primary prevention in CVD in trials and cohort studies, Whitlock et al (2016) found that using aspirin ≤100 mg in CVD primary prevention increased the odds of GI bleeding (OR=1.58, 95% CI 1.29-1.95, I\(^2\)=28.6%) but there were nonsignificant increased odds of hemorrhagic stroke (OR=1.27, 95% CI 0.96-1.68, I\(^2\)=0%).\(^{33}\) The pooled estimate for hemorrhagic stroke was likely due to fewer events, and
for both pooled estimates the results were not statistically heterogenous or precise which may have been due to inadequate power.

The risk of bleeding depends considerably on patient-related factors; individuals can have a high baseline risk of bleeding or factors that greatly enhance aspirin associated bleeding. For example, it is well known that older age is associated with an increased risk of major GI bleeding.\textsuperscript{34} Whitlock et al (2016) found that increasing age is the strongest independent risk factor for increased GI bleeding with any aspirin dose (aRR=2.15, 95% CI 1.93-2.39, per decade), while smoking and mean blood pressure were the strongest independent risk factors for hemorrhagic stroke with any aspirin dose [(aRR=2.18, 95% CI 1.57-3.02, per decade) and (aRR=2.18, 95% CI 1.62-2.87, per decade)].\textsuperscript{33} Concurrent use of other medications, such as NSAIDs, are known to enhance aspirin’s bleeding effect.\textsuperscript{34} Whitlock et al (2016) found that concurrent use of NSAIDs increased the baseline risk of major bleeding with any aspirin dose (aRR=1.10, 95% CI 1.05-1.16, per year).\textsuperscript{33} Individuals with the risks noted previously, however, are typically excluded from trials which may suggest an underestimation of risk.

The authors of this study did not evaluate the risk factors for increased bleeding by stratifying by aspirin dose, therefore they were unable to tell whether the dose has an effect on baseline bleeding risk as well. It is important to note that the authors of this review emphasized results from a more limited set of trials in order to use the same or similar aspirin regimens in applicable populations (primary prevention of CVD), which may have introduced imprecision due to a lack of power. It is also important to note that excess bleeding events are relatively rare and not consistently captured throughout trials, i.e. major GI or intracerebral bleeding tend to be reported but not minor bleeding issues.
Also, hemorrhagic and ischemic strokes are not reported separately in many trials. As some of the risk factors for preeclampsia overlap with risk factors for CVD (hypertension, diabetes, and obesity), we will monitor for these potential adverse events previously mentioned in our proposed study and will discuss further in Chapter 3.

The safety of aspirin during pregnancy has been extensively studied. In a 2014 systematic review and meta-analysis conducted by Henderson et al for the USPSTF, data from 19 RCTs and 2 observational studies was analyzed and limited evidence of harms associated with aspirin use in pregnancy was found. Overall pooled results showed no significant risk for placental abruption from low-dose aspirin (RR=1.17, 95% CI 0.93-1.48), however, the effect estimate was in the direction of harm. When stratified by preeclampsia risk, the pooled estimate of studies of women at an elevated risk of preeclampsia showed no increased risk of abruption (RR=1.12, 95% CI 0.86-1.46), nor did the estimate for studies of women at an average risk of preeclampsia (RR=1.38, 95% CI 0.84-2.28). The analysis also suggested there was no effect on perinatal mortality (RR=0.92, 95% CI 0.76-1.11), however, the possibility of increased perinatal mortality could not be completely ruled out due to power limitations to detect differences in such a rare outcome. For both perinatal mortality and placental abruption, estimates of increased risk approached clinical but not statistical significance, and were more strongly suggested in healthy populations at low or average risk of preeclampsia compared to high risk.

Henderson et al (2014) also found no increased risk of postpartum hemorrhage (RR=1.02, 95% CI 0.96-1.09) in a pooled analysis, and the result was the same regardless of the preeclampsia risk level. A pooled analysis also found no increased risk of intracranial hemorrhage in neonates (RR=0.84, 95% CI 0.61-1.16), however, the rarity
of the outcome limited the ability to detect treatment group differences. There were some notable limitations in this systematic review, one being that many of the harms evaluated and some of the benefits were rare outcomes which limits the ability to draw conclusions due to power constraints. Small study effects were also seen with some of the outcomes, and many small studies did not contribute to the pooled analysis due to no events of rare outcomes which may have contributed to the inconsistent results of the statistical tests for small study effects on these outcomes. Overall, however, this meta-analysis identified evidence demonstrating aspirin’s safety in pregnancy, which was a contributing factor in the recommendations released by the USPSTF and ACOG indicating that low-dose aspirin should be used for the prevention of preeclampsia.

A recent systematic review and meta-analysis conducted by Roberge et al (2018) aimed to look at the effect of aspirin used for the prevention of preeclampsia on placental abruption or antepartum hemorrhage. A total of 20 RCTs were included, and subgroup analyses were conducted based on aspirin dosage (<100 and ≥100 mg) and gestational age at onset of treatment (<16 and >16 weeks’ gestation). In the case of aspirin <100 mg, there was no significant effect on the risk of placental abruption or antepartum hemorrhage (RR=1.20, 95% CI 0.79-1.81, p=0.39), and there was no significant effect irrespective of gestational age [<16 weeks (RR=1.11, 95% CI 0.52-2.36, p=0.79) and >16 weeks [RR=1.32, 95% CI 0.73-2.39, p=0.35], p value between subgroups =0.72]. In the case of aspirin ≥100 mg, there was a nonsignificant reduction in the risk of placental abruption or antepartum hemorrhage with initiation ≤16 weeks (RR=0.62, 95% CI 0.31-1.26, p=0.19) and a nonsignificant increase in the risk of placental abruption or antepartum hemorrhage with initiation >16 weeks (RR =2.08, 95% CI 0.86-5.06, p=
There was, however, a significant difference between the subgroups (p=0.04), indicating a significant difference in the risk of placental abruption or antepartum hemorrhage between initiating treatment \( \leq 16 \) weeks’ gestation and \( >16 \) weeks.

This meta-analysis had some notable strengths, which include that all but one of the 20 studies were considered high quality studies and heterogeneity was low (\( I^2=0-29\% \)). Of note, limitations of this study include the potential risk of selection bias, as only 20 out of 65 studies screened that looked at the relationship between aspirin and the prevention of preeclampsia reported data for placental abruption or antepartum hemorrhage. This data was also reported as secondary outcomes in the trials, and although aspirin did not have a significant effect on these outcomes, the trials were not powered adequately for such an outcome. The authors were also not able to evaluate the effect of compliance because it was not reported in 8 of the 20 trials, and 10 of the remaining 12 trials did not report the results of compliance separately. The results of this study provided further evidence in favor of the safety of low-dose aspirin initiated \( \leq 16 \) weeks’ gestation, which is the recommendation put forth by ACOG for the prevention of preeclampsia in women at an increased risk.

Older case reports published have shown that higher doses of salicylates may cause adverse effects in breastfed infants, such as metabolic acidosis and thrombocytopenia. These reports were published in 1967 and 1981, and the mothers in these reports were taking over 3.9g of aspirin per day. In 2017, Datta et al sought to evaluate the transfer of acetylsalicylic acid (aspirin) and its metabolite, salicylic acid, into human milk following the use of low-dose aspirin. Milk samples were collected from seven women who were exclusively breastfeeding at time points between 0 and 24 hours.
following a steady state daily dose of 81mg aspirin. In all of the milk samples, acetylsalicylic acid levels were undetectable, which suggests that aspirin is rapidly cleared from the maternal plasma compartment. The maximum observed concentration of salicylic acid was 114.9ng/ml observed at 4 hours, and the calculated relative infant dose was 0.4%. No adverse effects or outcomes were reported for the infants.

This has been the only study to evaluate the steady state levels of low-dose aspirin and its transfer into human milk. It provided quantitative information on the potential dose that an infant might consume during breastfeeding. The results of this study show that low-dose aspirin penetrates the milk compartment minimally and is unlikely to have any clinical effect on the breastfed infant. It is important to note, however, that this study did not evaluate concentrations over a longer period of time. Therefore, we will monitor for any potential adverse effects in the breastfed infant in our proposed study, as well as any of the potential adverse events previously mentioned in this section, and we will discuss further in Chapter 3.

2.4 Confounding Variables

Baseline characteristic and demographic data including maternal age, gravidity, parity, BMI, race, sociodemographic status, medical history and previous obstetric history, are all important factors that may influence the development of postpartum preeclampsia. Their effect may be difficult to isolate and remains important to bear in mind when evaluating our data. Our proposed study will use randomization in an effort to minimize any statistically significant differences between study groups and minimize the effects of confounding. We will collect and report these characteristics, and will plan to
perform multiple logistic regression in the event that statistically significant differences between the groups are found.

Concomitant use of other medications may have the potential to act as confounders. Recently, it has been postulated that statins may have a role in preventing preeclampsia due to their mechanism of promoting the release of VEGF and PIGF, and reducing sFlt1 and sEng levels. A systematic review published this year found contradictory effects of statins on blood pressure, and sFlt1 and sEng levels in preeclampsia. With increasing rates of obesity, hypertension and diabetes, many women who are at increased risk of developing preeclampsia may be taking a statin prior to pregnancy or postpartum. While we anticipate effects from statins to be minimal, we will consider statin use in pregnancy or the postpartum period as a potential confounder.

Lastly, gestational hypertension may have the ability to act as a confounder on the development of preeclampsia. While diagnostically a separate entity, 15-46% of women initially diagnosed with gestational hypertension will develop preeclampsia, indicating there may be a spectrum of pregnancy induced hypertension. Therefore, we will also consider gestational hypertension as a potential confounder in our study as the intervention being evaluated, aspirin prevention, has only been proven to prevent preeclampsia and not pregnancy induced hypertensive disorders on the whole.

2.5 Review of Relevant Methodology

2.5.1 Study Design

In the current data, there are no published studies that look at the use of prophylactic low-dose aspirin on the prevention of postpartum preeclampsia in women who are at an increased risk of developing preeclampsia. The limited literature published
about postpartum preeclampsia has sought to evaluate the pathophysiology, clinical course, associated risk factors, and management\cite{13,16,23,41-45}; and have been retrospective in nature. Some studies have sought to compare antepartum and postpartum preeclampsia to determine similarities and/or differences.\cite{14-16,30} A few studies have examined postpartum hypertension\cite{18,24}, and have also been retrospective studies. Current literature suggests that postpartum preeclampsia may have the same pathophysiology as antepartum preeclampsia\cite{16,18,30}, as well as similar risk factors.\cite{17}

Low-dose aspirin prophylaxis during pregnancy until delivery is the current standard of care for the prevention of preterm preeclampsia.\cite{7} If the pathophysiology of postpartum preeclampsia is similar to that of antepartum preeclampsia, then it is worthwhile to investigate whether continuing aspirin until 6 weeks postpartum may have an effect on the incidence of new onset postpartum preeclampsia. There have been many randomized, double-blind, placebo controlled trials published that have examined the efficacy of low-dose aspirin in the prevention of preeclampsia.\cite{28,29,46,47} Therefore, in order to obtain robust data and determine a causal relationship between the intervention and primary outcome while minimizing the effect of bias and confounding variables, we propose a multi-center, double-blind, placebo-controlled randomized trial. Further details regarding study methods and approach will be discussed in Chapter 3.

2.5.2 Study Population and Selection Criteria

In trials that have evaluated the efficacy of aspirin in reducing the incidence of preeclampsia, some investigators have used maternal medical and personal risk factors to identify patients\cite{27,28,47,48}, while some used a combination of maternal risk factors and screening algorithms that use biophysical and biochemical measurements such as uterine-
artery pulsatility index, mean arterial pressure, and maternal serum pregnancy-associated plasma protein A and PlGF. In the U.S., both ACOG and the USPSTF recommend initiating 81mg aspirin daily between 12-28 weeks’ gestation (optimally before 16 weeks) in women with 1 or more high risk factor or 2 or more moderate risk factors for preeclampsia. High risk factors include history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, or autoimmune disease (systemic lupus erythematosus or antiphospholipid syndrome), and moderate risk factors include nulliparity, obesity (BMI > 30), family history of preeclampsia (mother or sister), sociodemographic characteristics (African American race, low socioeconomic status), age >35 years, or personal history factors (low birthweight or small for gestational age, previous adverse pregnancy outcome, >10 year pregnancy interval). While the recommendations from ACOG and USPSTF have a disadvantage of not basing treatment recommendations on an individualized risk assessment, they do have the advantages of being relatively easily and inexpensive to implement. In our proposed study, we will use the guidelines set forth by ACOG and USPSTF as our inclusion criteria in order to ensure our results can be applicable to obstetric practice in the U.S.

The prevalence of preeclampsia in the U.S. ranges from 3-8%. Within the last 20 years, the incidence of preeclampsia has been increasing, largely due to increasing rates of obesity, diabetes, and hypertension. Since 1999, there has been an increasing trend in obesity in the U.S. The prevalence of obesity in 2017-2018 among U.S. women ages 20-39 was 39.7% and ages 40-59 was 43.3%. In 2017-2018, the prevalence of hypertension in U.S. women ages 18-39 was 13% and ages 40-59 was 49.9%.
Approximately 1-5% of pregnancies are affected by chronic hypertension\textsuperscript{54}, and that percentage is expected to continue increasing.\textsuperscript{1} The prevalence of diabetes mellitus in U.S. women of reproductive age has been reported to be 3.1-6.8\%\textsuperscript{55}, and pregestational diabetes has been observed in 1-2\% of all pregnancies.\textsuperscript{56}

Among U.S. adults ages 18-44, 6\% have chronic kidney disease (CKD) and 14.3\% are women.\textsuperscript{57} Women with CKD have 10 times the risk of preeclampsia compared to women without CKD, and preeclampsia occurs in up to 40\% of women with CKD.\textsuperscript{58} It is estimated that 161,000-322,000 U.S. adults have systemic lupus erythematosus, and 9 out of 10 diagnoses are in women ages 15-44 who are of child-bearing age\textsuperscript{59,60}. The prevalence of antiphospholipid syndrome is estimated to be 2\% in women with uncomplicated pregnancies and 10-20\% of pregnancies with a Great Obstetrical Syndrome (preeclampsia, intrauterine growth restriction, preterm labor, preterm prelabor rupture of membranes, and fetal demise).\textsuperscript{61} Preeclampsia is more prevalent in African American women than white women\textsuperscript{1}, and may be in part due to African American women being disproportionately affected by risk factors for preeclampsia.\textsuperscript{62} With this data on the different risk factors for preeclampsia, we anticipate that we will have access to enough patients to enroll in our proposed study. Further details on the study population and sample size will be discussed in Chapter 3.

Exclusion criteria in the literature have included bleeding disorders (such as Von Willebrand's disease, hemophilia, and thrombophilia); active peptic ulcer disease; asthma; hypersensitivity to aspirin, NSAIDs, or other salicylates; nasal polyps; congenital anomalies; and aspirin use prior to trial.\textsuperscript{27-29,46-49} Because aspirin can damage GI mucosa and cause ulcers and bleeding, women with peptic ulcer disease are generally excluded.
from these studies as they are at an even greater baseline risk of bleeding.\textsuperscript{32} Women with bleeding disorders have also typically been excluded due to aspirin’s increased risk of bleeding.\textsuperscript{33,34} There is significant cross-sensitivity between aspirin and other nonsteroidal drugs (such as NSAIDs), therefore anyone with a hypersensitivity to NSAIDs is typically excluded as well. Aspirin exposure in patients with nasal polyps may induce life-threatening bronchoconstriction\textsuperscript{63}, as well as in patients with asthma who have a history of aspirin-induced bronchoconstriction.\textsuperscript{64} In our proposed study, we will use similar exclusion criteria as previous studies, including those that are most applicable and relevant to our study population. More details will be included in Chapter 3.

2.5.3 Intervention Dose and Timing

Aspirin’s preferential inhibition of COX-1 at lower doses (≤150mg)\textsuperscript{12} led to the research into and subsequent recommendations for its use in preventing preeclampsia. The majority of trials examining aspirin’s effect on preeclampsia have initiated treatment between 12-28 weeks’ gestation\textsuperscript{12}, and optimal results have been seen when treatment is started ≤16 weeks’ gestation\textsuperscript{65,66}. In a 2017 meta-analysis, Roberge et al found that low-dose aspirin (≤150mg) initiated at ≤16 weeks’ gestation was associated with a significant reduction in the prevalence of preeclampsia (RR=0.57, 95% CI 0.43-0.75, p<0.001), however, there was some heterogeneity observed between studies (I\textsuperscript{2}=52%).\textsuperscript{67} Low-dose aspirin initiated >16 weeks’ gestation was associated with a modest reduction in the prevalence of preeclampsia (RR=0.81, 95% CI 0.66-0.99, p=0.04).\textsuperscript{67} When comparing the two most studied doses, aspirin 100mg vs 60mg was significantly more effective in the reduction of preeclampsia when initiated ≤16 weeks’ gestation [(RR=0.48, 95% CI 0.31-0.74) vs (RR=0.93, 95% CI 0.75-1.15); p<0.001].\textsuperscript{67} These results were similar to
previous meta-analyses that found that low-dose aspirin initiated ≤16 weeks’ gestation in high risk women reduced the prevalence of preeclampsia.65,68 Of note, a major limitation in this meta-analysis is the absence of large RCTs that recruited participants ≤16 weeks’ gestation; most data in the analysis came from small and moderate RCTs or from subgroups of participants recruited in larger RCTs which may have introduced potential biases and overestimated treatment effect.

A recent RCT conducted by Gu et al (2020) comparing placebo and 25mg, 50mg, and 75mg aspirin in high risk Chinese women found that aspirin significantly reduced the incidence of preeclampsia and that there was a linear relationship between the dosage of aspirin and the incidence of preeclampsia – as aspirin dosage increased the incidence of preeclampsia decreased (p<0.05).47 This was a novel study looking at the dose dependent effect of aspirin on preeclampsia in China, however the results may not be generalizable to a U.S. population. Another recent double-blind RCT conducted by Kumar et al (2020) comparing 150mg vs 75mg aspirin started between 11-14 weeks’ gestation in Indian women at high risk of developing preeclampsia found a significant difference in the incidence of preeclampsia between the two groups (6.5% vs 17.2% respectively, p=0.046).46 This study, however, had a small sample size (n=190) which may have led to a small study effect that overestimated the effect size. Also, because India is a developing country, the incidence of preeclampsia in the study population may be higher than the incidence in the U.S. and the higher dosage of aspirin may not have the same effect in our proposed study population.

Trials that have evaluated the time-dependent effects of low-dose aspirin on blood pressure in pregnant women have found that there was a substantial benefit when aspirin
was taken later in the day. Both Hermida et al (1997) and Ayala et al (2013) found that a blood pressure lowering effect is achieved when low-dose aspirin is taken at bedtime but not when taken upon awakening.\textsuperscript{69} In the U.S., aspirin tablets are produced in dosages of 75mg, 81mg, 162mg, and 325mg\textsuperscript{70}, and both ACOG and the USPSTF recommend using 81mg aspirin in preeclampsia prevention.\textsuperscript{12,50} Therefore, in our proposed study, our intervention will be 81mg aspirin taken daily at bedtime.

2.5.4 Outcomes and Statistical Analysis

Prior studies that have examined the relationship between low-dose aspirin and preeclampsia have designated the development of preeclampsia (incidence) in study groups as the primary outcome, operationalized as a dichotomous outcome and analyzed using the chi-squared test.\textsuperscript{27-29,46,47,49} Because the data on postpartum preeclampsia is extremely varied throughout the literature\textsuperscript{24,71,72}, the primary outcome in our proposed study will be the development of new onset postpartum preeclampsia in order to have an accurate estimate of the incidence in our study population. Similar to previous studies, our outcome will be dichotomous and will be analyzed using the chi-squared test.

Adverse maternal outcomes related to postpartum hypertension and/or preeclampsia have also been examined in several studies.\textsuperscript{17,24,45} These include readmission to the hospital, requiring ICU level care, the use of magnesium sulfate, the development of postpartum eclampsia or stroke, IV anti-hypertensive medication needed, and anti-hypertensive medication required at discharge, and have been operationalized as dichotomous outcomes analyzed with the chi-squared test.\textsuperscript{17,24,45} In our proposed study, we will evaluate these adverse maternal outcomes as secondary outcomes and analyze the results using the chi-squared test similar to previous studies in order to evaluate whether
continuing aspirin until 6 weeks postpartum will have an effect on these outcomes. Further details regarding proposed statistical analysis will be detailed in Chapter 3.

2.6 Conclusion

The current literature regarding postpartum preeclampsia is limited, mostly involving retrospective studies, and supports the need for further studies to increase our understanding of postpartum preeclampsia. Low-dose aspirin, the current recommended standard of care for the prevention of antepartum preeclampsia, has been extensively studied in pregnancy and has been found to be safe with regards to maternal and neonatal adverse outcomes. With recent evidence indicating postpartum preeclampsia may share the same pathophysiology as antepartum preeclampsia, the results of a RCT that explore the relationship between continued aspirin usage postpartum and its effect on preventing postpartum preeclampsia will help to fill in the gap in the current literature and guide recommendations to women who are at increased risk of developing the disease.
References


CHAPTER 3: STUDY METHODS

3.1 Study Design

We propose a multi-center, double-blinded, randomized placebo-controlled trial to determine if there is a difference in the incidence of new onset postpartum preeclampsia in women who receive 81mg aspirin once daily initiated within 24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum compared to placebo. The study will take place at the 12 clinical centers and their associated subsites within the Maternal Fetal Medicine Units (MFMU) Network. The MFMU Network was established in 1986 to conduct clinical research aimed at improving maternal and perinatal outcomes in a cost-effective and timely manner.1 A large network such as MFMU, which covers over 160,000 deliveries a year through its 12 clinical centers, is needed to answer such a specific clinical question as the one proposed in our study. The MFMU Network consists of a racially, ethnically, and geographically diverse population that will also make our study results more generalizable to the United States (U.S.) population.1

Yale New Haven Hospital (YNHH) is a subsite of the Brown University clinical site, and will serve as the main site for the principal investigator. Study personnel and subjects will be blinded to the intervention in order to minimize observational and reporting bias. Confounders between the two groups should be controlled for via the randomized controlled trial (RCT) design; however, any residual confounding or imbalance between the study groups will be addressed by performing multiple logistic regression.
3.2 Study Population and Sampling

The study population under investigation will be pregnant women who are seen by obstetric providers within the MFMU Network’s 12 clinical sites and associated subsites. The study will utilize a consecutive convenience sampling method to ensure that the study sample more likely represents the target population. All pregnant women presenting for a prenatal care visit between 12-16 weeks’ gestation who are deemed eligible according to pre-established criteria will be asked to participate.

The inclusion criteria for the selected study population is pregnant women ≥ 18 years of age, pregnancy gestational age 12-16 weeks at the time of enrollment, who have one or more of the following high risk factors: history of preeclampsia; multifetal gestation; chronic hypertension; type I or II diabetes; renal disease; or autoimmune disease such as systemic lupus erythematosus or anti-phospholipid syndrome; or 2 or more of the following moderate risk factors: nulliparity, obesity (BMI > 30), family history of preeclampsia (mother or sister), sociodemographic characteristics (African American race, low socioeconomic status), age ≥ 35 years, and personal history factors (low birthweight or small for gestational age, previous adverse pregnancy outcome, >10 year pregnancy interval).

Exclusion criteria include major fetal abnormality or genetic anomaly identified at the time of screening; bleeding disorders such as Von Willebrand’s disease, hemophilia, or a thrombophilia; hypersensitivity to aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and other salicylates; aspirin-induced asthma; nasal polyps; active peptic ulcer disease.

3.3 Subject Protection and Confidentiality
This study will be submitted to the MFMU and Yale University Institutional Review Boards (IRB) for approval. The study will comply with all requirements set forth by the IRB, and all procedures and regulations outlined in IRB policy 330 concerning human research involving pregnant women, who are considered a vulnerable population. Members of the research team will not have any financial or non-financial relationships with the research topic in order to avoid any conflict of interest. Eligible women will be fully informed and evaluated for their capacity to provide informed consent. Participation will be free of coercion and voluntary. Informed, written consent will be obtained from all eligible study participants (Appendix A). Our consent will explicitly detail the purpose of the research study, all procedures that will take place, anticipated duration, and all of the potential benefits and risks of participation.

Confidentiality and privacy practices will be thoroughly explained to all subjects. Participants will be notified of their right to drop out of the study at any time without notice or explanation, and will be assured that it will not affect their obstetrical care. All members of the research team will complete the mandatory Human Subjects Protection Training, Good Clinical Practice Training, and HIPAA privacy training. Patient information will only be accessed by the research team members through dedicated secure computers that will be given to each site with password protection. Each participant will be assigned a unique identification code to be used throughout the study.

3.4 Recruitment

The study will recruit pregnant women through the 12 MFMU clinical centers and their associated subsites over the course of 13.5 months. These sites will receive notice of the trial and obstetric providers will be asked to screen patients to determine eligibility
according to the inclusion and exclusion criteria. Recruitment flyers for the study will also be posted at the clinical centers and subsites, and will be translated to Spanish (Appendix B). Women who agree to participate will be contacted by a member of the research team via telephone or at a routine prenatal care visit. Using the inclusion and exclusion criteria, members of the research team will interview these women to confirm eligibility. Women meeting criteria will be offered enrollment in the study and will be fully informed of the study details, procedures and risks. A member of the research team will consent eligible subjects between 12-16 weeks’ gestation with the goal of randomization to occur at delivery. During the period of time between consent and randomization, a research assistant will review medical records to collect pregnancy data, including the development of antepartum preeclampsia or gestational hypertension. Following standard of care guidelines, participants will attend their regular prenatal care visits and receive 81mg aspirin prophylaxis during the pregnancy administered by their obstetric provider.

3.5 Study Variables and Measures

3.5.1 Independent Variable

The independent variable in this study is 81mg aspirin in the postpartum period. The intervention will be given as an 81mg aspirin tablet or an identical appearing placebo tablet starting within 24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum. The timeframe for aspirin initiation allows for any delivery complications to be addressed prior to starting, as well as ensuring participants have started aspirin prior to discharge from the hospital. The intervention and placebo will be produced and distributed by the Investigational Pharmacies at each clinical center in the
MFMU Network in bottles containing 30 tablets at a time. Enough bottles will be
dispensed at each in person study visit to last until the next in person visit.

The intervention will be given as 81mg aspirin as it is readily available in the US
and cost effective; therefore, if the results of the study are significant it will be applicable
to most practices. The 81mg dose was selected because its safety profile has been
extensively studied in pregnancy. The active ingredient is 81mg acetylsalicylic acid, and
inactive ingredients include carnauba wax, cornstarch, hypromellose, powdered cellulose,
and triacetin. The placebo tablet will be identical in appearance and will contain the
same inactive ingredients as the intervention (carnauba wax, cornstarch, hypromellose,
powdered cellulose, and triacetin) but will not contain the active ingredient
(acetylsalicylic acid).

The intervention and placebo tablets will be produced in the exact same protocol
by the Investigational Pharmacies at each clinical center in the MFMU network. They
will be identical in appearance and packaged in trial product bottles that are also
identical. Each tablet will be self-administered at bedtime by the subject starting within
24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum.
Previous studies have found that administering aspirin at bedtime was associated with a
significantly reduced systolic and diastolic blood pressure compared to administering
upon awakening. Bottles will be returned at each in person study visit and tablets will
be counted to assess adherence and compliance.

3.5.2 Dependent Variable

The dependent variable and primary outcome in this study is new onset
postpartum preeclampsia defined as new or worsening hypertension with a systolic blood
pressure \( \geq 140 \text{ mmHg} \) and/or a diastolic blood pressure \( \geq 90 \text{ mmHg} \) \textit{on at least 2 occasions at least 4 hours apart at any time starting after 2 days postpartum until 6 weeks postpartum in a previously normotensive patient}, and the new onset of 1 or more of the following: proteinuria \( \geq 0.3 \text{ g} \) in a 24-hour urine specimen or protein/creatinine ratio \( \geq 0.3 \text{ (mg/mg) (30 mg/mmol)} \) in a random urine specimen or dipstick \( \geq 2+ \) if a quantitative measurement is unavailable; platelet count \(< 100,000/\text{microL} \); serum creatinine \( > 1.1 \text{ mg/dL (97.2 micromol/L)} \) or doubling of the creatinine concentration in the absence of other renal disease; liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory; pulmonary edema; new-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics; or visual symptoms (e.g., blurred vision, flashing lights or sparks, scotomata). The primary outcome will be operationalized as a dichotomous outcome. Women will be classified as either having developed the outcome of interest or not having developed the outcome of interest. A participant that develops antepartum preeclampsia during the pregnancy will not be counted as having developed the outcome of interest.

Secondary outcomes in this study will include postpartum readmission to a hospital, postpartum eclampsia, use of magnesium sulfate, IV anti-hypertensives needed, ICU level care needed, stroke, anti-hypertensive medication required at discharge, gestational hypertension with postpartum preeclampsia, and antepartum preeclampsia with postpartum preeclampsia. These outcomes will be measured during the postpartum period until 6 weeks postpartum, which is the period of time defined for which postpartum preeclampsia can develop. All secondary outcomes will be operationalized as
dichotomous outcomes. Women will be classified as either having developed the secondary outcome of interest or not having developed the secondary outcome of interest.

3.5.3 Potential Confounding Variables

Baseline characteristic and demographic data including maternal age, gravidity, parity, BMI, race, medical and obstetric history have the potential to act as confounders in this study. The use of randomization should minimize the confounding effects of these factors. All potential baseline confounding variables will be assessed in a participant survey during the initial study visit (Appendix C). Gestational hypertension and statin use during pregnancy or the postpartum period may also be potential confounders. If needed, multiple logistic regression will be conducted during data analysis in order to control for possible confounding variables.

| Table 1. Descriptive Characteristics of Study Population |
|---------------------------------|-----------------|------------------|
| Characteristic                  | Variable        | Description                  |
| Maternal Age                    | Continuous      |                               |
| Gravidity                       | Continuous      |                               |
| Parity                          | Continuous      |                               |
| Gestational Age at Randomization| Continuous      |                               |
| Pre-pregnancy BMI               | Continuous      | Yes, No                       |
| Multifetal Gestation            | Dichotomous     | Yes, No                       |
| Race                            | Categorical     | White, Black, Asian, American Indian or Alaska Native, Pacific Islander |
| Ethnicity                       | Categorical     | Hispanic or Latino, Non-Hispanic |
| Marital Status                  | Categorical     | Single, Married, Separated, Divorced, Widowed |
| Medical History                 | Categorical     | Chronic Hypertension, Type 1 Diabetes, Type 2 Diabetes, Systemic Lupus Erythematosus, Antiphospholipid Syndrome, Kidney Disease |
| History of Preeclampsia         | Dichotomous     | Yes, No                       |
| Family History of Preeclampsia  | Dichotomous     | Yes, No                       |
| Previous Use of Statins         | Dichotomous     | Yes, No                       |
3.6 Additional Methodology Considerations

3.6.1 Study Protocol

Enrollment and consent will occur between 12-16 weeks’ gestation, and participants will be randomized at time of delivery. The period of time between consent and randomization will be used for medical record review and data collection including pregnancy outcomes, development of gestational hypertension or antepartum preeclampsia, and gestational age at delivery. During the pregnancy, participants will be given 81mg aspirin prophylaxis by their obstetric provider following standard of care guidelines up until delivery. After randomization, participants will take one trial product tablet every night at bedtime starting within 24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum. Participants will receive a handheld tablet on which they will receive a nightly reminder to take their trial product and will also complete a brief daily questionnaire which will assess if they took that evening’s dose and any possible adverse events (Appendix D). The handheld tablet will be returned at each in person study visit and data will be transferred to the study specific software. Subjects will also return trial product bottles at each in person visit so that compliance can be calculated.

Study participants will have research visits to screen for symptoms, measure blood pressure, obtain blood and urine analysis, monitor adverse events and assess compliance from the time of enrollment until 6 weeks postpartum. When possible, these visits will be combined with the participant’s routine prenatal and postpartum appointments as directed by their primary obstetric provider. In person research visits will occur at 12-16 weeks’ gestation (initial visit for enrollment and consent), at time of
delivery (randomization), 1 week postpartum, 2 weeks postpartum, and 6 weeks postpartum. A telephone research visit will occur at 4 weeks postpartum.

3.6.2 Randomization and Assignment of Intervention

Randomization will occur at time of delivery for all study subjects. All eligible women will be block randomized into two study arms via specialized computer software using random block sizes in order to maintain balance between the treatment arms and reduce the opportunity for bias and confounding. The allocation will be concealed so that investigators will not know which participant will go into each study group. Subjects will be randomized into either the intervention arm or placebo arm. Each participant will receive a unique randomization number, and after randomization each participant will be assigned a random number through the computer software that correlates with specific trial product bottles. Participants will receive the assigned trial product and will receive instructions to take one tablet every night starting within 24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum, and complete their daily questionnaire on the handheld tablet.

3.6.3 Blinding

In our proposed study, both participants and investigators/research staff will be blinded to the intervention during the treatment and data collection periods. The intervention and placebo tablets will be identical, making it impossible for the participants and investigators to discern which tablet is the active one based on appearance. This robust blinding will minimize any bias and ensure internal validity.

3.6.4 Adherence
Adherence to protocol will be assessed in 2 ways. The subjects will return the trial product bottles at each in person visit so that a member of the research team can evaluate for any missed doses by counting pills. Use of $\geq 85\%$ of the prescribed doses will be considered adequate compliance. Additionally, subjects will receive a handheld tablet on which they will complete a daily questionnaire that logs any missed doses and adverse events. Subjects will be able to set an alarm on the tablet that reminds them to take the trial product and complete the questionnaire for the day.

3.6.5 Monitoring Adverse Events

We expect that adverse outcomes in this study will be rare. As discussed in the literature review, aspirin penetrates the milk compartment minimally and is unlikely to have any clinical effect on the breastfed infant.\(^7\) Low-dose aspirin also moderately increases the risk of GI bleeding but not hemorrhagic stroke.\(^8\) Although we will be excluding women with an allergy to aspirin or other salicylates, we will monitor for any signs or symptoms of hypersensitivity, such as urticaria, or anaphylaxis. We will also monitor for any systemic adverse reactions, such as abdominal pain, nausea, vomiting, heartburn, headache, dizziness, tachypnea, bronchospasm, GI bleeding, or hemorrhagic stroke.

At every study visit, we will assess whether subjects have experienced any adverse events. In their daily questionnaire on the handheld tablet, subjects will record whether they have experienced any adverse events such as those listed previously or any other symptoms they may experience. In the event that an adverse outcome does occur, a member of the research team will complete an adverse event report form that will be submitted electronically for review. It will be at the investigator’s discretion whether the
subject should continue in the study or not. We will also have a safety monitoring board independent from the trial that will review all adverse events that occur and assess whether the study should be stopped.

3.7 Data Collection

We will begin collecting data through a participant survey at the initial study visit that will be administered by a research assistant. The survey will assess baseline characteristic and demographic data including maternal age, gravidity, parity, BMI, medical history, social history, obstetrical history, and sociodemographic characteristics. This data will be used to analyze descriptive and potential confounding factors. At each in person study visit, maternal blood pressure will be measured using standardized blood pressure cuffs that will be distributed to each study site. Study coordinators will receive training on how to measure each subject’s blood pressure using an exact protocol to reduce variability between measurements. A urine specimen will be collected for analysis of proteinuria, and blood samples will be drawn to measure platelet count, serum creatinine, liver transaminases, sFlt1 and PIGF.

For telephone study visits, study coordinators and/or research assistants will administer a survey that will evaluate a participant’s compliance with the trial product and any adverse events (Appendix E). Medical records will be assessed to collect data during the pregnancy (development of antepartum preeclampsia or gestational hypertension, gestational age at delivery), and will also be used to determine whether significant maternal or neonatal adverse events occur, including placental abruption, postpartum hemorrhage, ductus arteriosus closure, neonatal intracranial hemorrhage, IUGR, congenital anomalies, and perinatal mortality. The research assistants assigned to
maternal and neonatal record retrieval will be blinded to the intervention status. All subject information for this study will be entered into electronic case report forms that members of the research team will access through the secure study-specific computers assigned to each site. These case report forms will be the source documents of the study that will be available for inspection by the regulation authorities.

3.8 Sample Size Calculation

The primary outcome of the proposed study is the incidence of new onset postpartum preeclampsia. We will test the two-sided null hypothesis that there is no difference in the incidence of new onset postpartum preeclampsia between 81mg aspirin prophylaxis administered once daily starting within 24 hours from birth up to 2 days postpartum and continued until 6 weeks postpartum compared to placebo.

Literature search performed could not find specific data regarding the incidence of new onset postpartum preeclampsia in high risk groups. A recent study reported that 10% of normotensive pregnancies developed de novo postpartum hypertension. These results were in line with another study conducted in 2015 that found that 9.9% of normotensive pregnancies developed de novo postpartum hypertension. These studies, however, do not specify whether the subjects were taking aspirin throughout pregnancy. A recent Chinese study reported a 9.6% incidence of antepartum preeclampsia in high risk pregnant women receiving 75mg aspirin beginning at 12 weeks’ gestation and continued until delivery. Using the data from these studies, we anticipate a 10% incidence of new onset postpartum preeclampsia in women at increased risk of developing preeclampsia in the placebo group.
A recent study evaluating the use of aspirin during pregnancy found that high-risk pregnant women who used aspirin for more than 7 days in the first trimester had a 24% lower risk of term preeclampsia compared to women who did not use aspirin. Another study conducted in China found a risk reduction of 20% in the incidence of preeclampsia in high-risk pregnant women using 100mg aspirin once daily during pregnancy until 34 weeks’ gestation. A systematic review and meta-analysis conducted in 2014 for the USPSTF determined that low-dose aspirin administered after the first trimester to pregnant women at elevated risk of preeclampsia had a 24% risk reduction; however, a small-sample bias on the treatment effect may have occurred, with the two largest RCTs estimating a 10% reduction. A large network like the MFMU will allow our study to recruit enough participants for a larger sample size in order to ensure adequate statistical power to detect clinically important differences and avoid small-sample bias. Using the data from these studies and meta-analysis, we hypothesize a 24% effect size and anticipate a 7.6% incidence of new onset postpartum preeclampsia in women at increased risk using 81mg aspirin in the postpartum period.

Our sample size was calculated to require a minimum sample size of 4,374, yielding 2,187 in each treatment arm using an estimated effect size of 24%, a power of 80% and a significance level (α) of .05 (two-tailed). This calculation was derived using the algorithm from Power and Precision Software (BioStat Inc.). Prior studies have shown loss to follow up and dropout rates up to 6%. We will adjust our sample size for a 10% attrition rate, therefore a sample size of 4,812 will be used in this study.

3.9 Statistical Analysis
The main statistical analysis will be performed using the intention to treat principle to minimize bias and allow for better generalizability. The variables that will be measured at baseline for the study groups include maternal age, race, ethnicity, marital status, gravidity, parity, multifetal gestation, pre-pregnancy BMI, history of preeclampsia, family history of preeclampsia, and use of statins (see Table 1). Continuous variables will be compared using the student t-test, and categorical and dichotomous variables will be compared using the chi-squared test. Any variable that exhibits a statistically significant difference between the 2 groups will be used in multiple logistic regression analysis to control for confounding.

<table>
<thead>
<tr>
<th>Table 2. Data Collection, Demographic Information</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Maternal Age (year) – mean (SD)</td>
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<tr>
<td>Gestational Age at Randomization (weeks) – mean (SD)</td>
</tr>
<tr>
<td>Gravidity – mean (SD)</td>
</tr>
<tr>
<td>Parity – mean (SD)</td>
</tr>
<tr>
<td>Pre-pregnancy BMI – mean (SD)</td>
</tr>
<tr>
<td>Multifetal Gestation</td>
</tr>
<tr>
<td>Yes – N (%)</td>
</tr>
<tr>
<td>No – N (%)</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White – N (%)</td>
</tr>
<tr>
<td>Black – N (%)</td>
</tr>
<tr>
<td>Asian – N (%)</td>
</tr>
<tr>
<td>Native American or Alaska Native – N (%)</td>
</tr>
<tr>
<td>Pacific Islander – N (%)</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Hispanic or Latino – N (%)</td>
</tr>
<tr>
<td>Non-Hispanic – N (%)</td>
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<tr>
<td>Marital Status</td>
</tr>
<tr>
<td>Single – N (%)</td>
</tr>
<tr>
<td>Married – N (%)</td>
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<tr>
<td>Separated – N (%)</td>
</tr>
<tr>
<td>Divorced – N (%)</td>
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<tr>
<td>Widowed – N (%)</td>
</tr>
</tbody>
</table>
To evaluate the primary outcome, we will determine the incidence of new onset postpartum preeclampsia with a 95% confidence interval. We will use the chi-squared test to analyze the primary outcome between the 2 study groups. To evaluate the secondary outcomes, we will also use the chi-squared test. If needed, we will perform multiple logistic regression. Results will be reported as mean ± standard deviation (SD) for continuous variables and percentages for categorical and dichotomous variables. A P value of 0.05 or less will be considered statistically significant. All analyses will be performed using the Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL).

<table>
<thead>
<tr>
<th>Medical History</th>
<th></th>
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<tbody>
<tr>
<td>Chronic Hypertension – N (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Type 1 Diabetes – N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes – N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus – N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid Syndrome – N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Disease – N (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>History of Preeclampsia</td>
<td>Yes – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History of Preeclampsia</td>
<td>Yes – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of Statins</td>
<td>Yes – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No – N (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To evaluate the primary outcome, we will determine the incidence of new onset postpartum preeclampsia with a 95% confidence interval. We will use the chi-squared test to analyze the primary outcome between the 2 study groups. To evaluate the secondary outcomes, we will also use the chi-squared test. If needed, we will perform multiple logistic regression. Results will be reported as mean ± standard deviation (SD) for continuous variables and percentages for categorical and dichotomous variables. A P value of 0.05 or less will be considered statistically significant. All analyses will be performed using the Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL).

<table>
<thead>
<tr>
<th>Table 3. Outcomes According to Trial Group</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Primary Outcome</td>
</tr>
<tr>
<td>New Onset Postpartum Preeclampsia – N(%)</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
</tr>
<tr>
<td>Medical Condition</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Postpartum readmission to a hospital</td>
</tr>
<tr>
<td>Postpartum eclampsia</td>
</tr>
<tr>
<td>Use of magnesium sulfate needed</td>
</tr>
<tr>
<td>IV anti-hypertensives needed</td>
</tr>
<tr>
<td>ICU level care needed</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Anti-hypertensive medication required at discharge</td>
</tr>
<tr>
<td>Gestational hypertension with postpartum preeclampsia</td>
</tr>
<tr>
<td>Antepartum preeclampsia with postpartum preeclampsia-N</td>
</tr>
</tbody>
</table>

### 3.10 Timeline and Resources

The proposed study will be conducted within two years once it has been approved by the IRB. The first 13.5 months will be used for recruitment of eligible pregnant women. The study protocol will take place over 8.5 months for each subject over the course of their pregnancy from the time of consent up to 6 weeks postpartum. Participants will not be recruited within the last 10.5 months to ensure that they will have completed the study in time for the two-year limit. We will complete all data analysis and report our findings in two months. Proposed study personnel will include: a single principal investigator and one co-principal investigator to oversee all operations; 12 physician sub-investigators trained in obstetrics located at each of the 12 MFMU Network’s clinical sites that will be responsible for all the women who will be participating in the study at that specific clinical site; 12 clinical research coordinators and 12 research assistants located at each of the 12 MFMU Network’s clinical sites for recruitment and data collection; and one physician and one physician associate student for data organization, statistical analysis, and reporting.
References

CHAPTER 4: CONCLUSION

4.1 Strengths and Advantages

4.1.1 Study Design

One of the major strengths of our study comes from its design - a multicenter, double-blind, placebo-controlled trial. The RCT design will allow us to establish the strongest possible evidence of causation. It will also decrease selection and observer bias, and minimize any potential confounders between the two study groups that would be due to an unequal distribution in the chosen population. By ensuring our proposed study is double-blinded, we hope it will limit outcome reporting bias. By using a placebo, we will be able to determine if improvement in the treated group is due to drug effect rather than the act of being treated.

4.1.2 Sample Size

Another strength of our proposed study is the large sample size. With a larger sample size, we will be able to identify any outliers that could skew the data in a smaller sample and provide a smaller margin of error leading to a more precise estimate. A larger sample size will also give us greater power to detect differences between the two study groups. By having our study take place within a large network like the MFMU, we will be able to screen and enroll the number of women needed to achieve our calculated sample size. We will also be able to make our study results more generalizable due to the diversity of patients seen within the MFMU network.

4.1.3 Feasibility and Practicality of Intervention

A major advantage of this study is that the intervention itself is readily available in the U.S. as a low cost, over-the-counter option. If the results of the study are
significant, there will be evidence in favor of a cost-effective treatment to use in the prevention of new onset postpartum preeclampsia. The intervention will be easy to implement and requires little time commitment from participants. This will aid in achieving high medication compliance with participants.

4.1.4 Novelty

The most significant strength of our study is its novelty. We will be able to fill in the gaps in the literature regarding new onset postpartum preeclampsia and its prevention. In the current literature, there is limited data regarding postpartum preeclampsia, its pathophysiology, clinical course, and treatment. Specifically, there have been no studies up to this point that have looked at ways to prevent it. Our study will be the first to look at preventing postpartum preeclampsia with the use of 81mg aspirin in the postpartum period. The results of this study have the potential to change current standard of care guidelines for obstetric patients who are at high risk for developing postpartum preeclampsia and further our understanding of this disease.

4.2 Limitations

4.2.1 Block Randomization

While our study addresses limitations in the current literature, there are still some limitations that we must note. One is the use of block randomization in our study design. With the use of block randomization, the allocation of participants may be predictable and result in selection bias. By using random block sizes instead of a specific block size, we hope to reduce any possible selection bias that may be introduced. Investigators and research staff will be kept blind to the size of the random blocks as well.

4.2.2 Cost and Time
Another is the cost and time associated with a RCT. Logistically, more resources are needed with such a large sample as the one needed for our study. The use of multiple sites may be difficult to organize and supervise. As such, this significantly increases the costs associated with conducting this study. The two-year timing of the study may also be a limitation. With only 13.5 months of recruitment available due to the longer treatment period needed to follow subjects throughout pregnancy and postpartum, we are left with a smaller amount of time to achieve our sample size goal. By conducting our study within a large network like the MFMU, however, we anticipate that we will be able to meet our goal within that time period.

4.2.3 Novelty

While the novelty of our study is a major strength, it also acts as a limitation. The literature search performed found limited data on postpartum preeclampsia. Specific data regarding the incidence and prevalence of new onset postpartum preeclampsia in the general population and our specific study groups was not found. Instead, we extrapolated data from other studies looking at similar populations, such as antepartum preeclampsia and de novo postpartum hypertension, to calculate our sample size. In order to compensate for this, if a subject develops antepartum preeclampsia, they will not be counted towards having developed the outcome of interest. This will allow for a more accurate representation of our outcome of interest and the ability of this study to further the understanding of postpartum preeclampsia in patient populations that are at an increased risk of developing the disease.

4.3 Clinical and Public Health Significance
Current research on postpartum preeclampsia is limited. There have been some retrospective studies that have looked at the placental findings of postpartum preeclampsia and found that they share a common pathophysiology with antepartum preeclampsia.\textsuperscript{1,2} No studies have been conducted that look at prevention of postpartum preeclampsia. As the first study to look at the relationship between low-dose aspirin in the postpartum period and the incidence of new onset postpartum preeclampsia, our study will be clinically significant and address an important question that has yet to be addressed in the current literature. The results of our study will either provide evidence to support or refute the continued use of low-dose aspirin until 6 weeks postpartum in the prevention of new onset postpartum preeclampsia.

Determining whether low-dose aspirin prophylaxis used during pregnancy can help reduce the incidence of new onset postpartum preeclampsia, and whether discontinuing at delivery or postpartum is more effective, may contribute to a decreased burden of the disease. Our results may help to prevent or lessen the maternal outcomes that can occur as a consequence of the disease and, in turn, improve public health.\textsuperscript{3,4} This study will also provide data for the conduction of evidenced-based medicine in practice and support future efforts for more research into the area of postpartum preeclampsia. Lastly, this study will bring awareness about the lesser known postpartum preeclampsia to providers working with pregnant populations and women in their reproductive age.
References

CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE
MATERNAL FETAL MEDICINE UNITS (MFMU) NETWORK

Study Title: Preventing postpartum preeclampsia with low-dose aspirin: a randomized controlled trial
Principal Investigator: Katherine Kohari, MD

Research Study Summary:
We are asking you to join a research study. The purpose of this study is to determine whether using low-dose aspirin during the postpartum period is effective in preventing postpartum preeclampsia. Study procedures will include: taking one pill every night for the duration of the study period, filling out a daily questionnaire, in person study visits where we will measure your blood pressure, obtain blood and urine samples for analysis, and telephone study visits in between in person visits. 5 in person visits and 1 telephone visits are required. In person visits will take 2 hours total.

We do not anticipate any significant risks in either study group. There are some general risks that may occur with the use of aspirin; however, these risks are extremely small. These include abdominal pain, nausea, vomiting, heartburn, dizziness, headache, tachypnea, and bronchospasm. We anticipate that women who use low-dose aspirin postpartum period will have less of a risk of developing postpartum preeclampsia. This will reduce the occurrence of adverse maternal outcomes, such as eclampsia, stroke, and long-term cardiovascular consequences.

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits. If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?
We are asking you to take part in this research study because your obstetrics provider identified you as being at an increased risk of developing preeclampsia. You also meet the following criteria: 18 years or older; pregnancy gestational age between 12 and 16 weeks; you are not allergic to aspirin or other salicylate medications; you do not have any
bleeding disorders, active peptic ulcer disease, nasal polyps, or asthma. We are looking for total of 4,812 participants to be part of this research study through 12 different sites.

**Who is paying for the study?**
The MFMU Network and Yale University School of Medicine will be providing monetary support for the study.

**What is the study about?**
The purpose of this study is to evaluate the efficacy of low-dose aspirin used during the postpartum period in the prevention of postpartum preeclampsia. Preeclampsia is a pregnancy complication characterized by high blood pressure and signs of damage to another organ system, such as your kidneys or liver. Antepartum preeclampsia can occur after 20 weeks’ gestation up until delivery. Postpartum preeclampsia can occur starting after birth up until 6 weeks postpartum. Some women can develop postpartum preeclampsia even without developing preeclampsia during their pregnancy. Current guidelines indicate that women who are considered at an increased risk of developing preeclampsia should be started on low-dose aspirin prior to 16 weeks’ gestation and continued up until delivery. In our study, we will be evaluating whether low-dose aspirin used during the postpartum period is effective in preventing postpartum preeclampsia.

**What are you asking me to do and how long will it take?**
If you agree to take part in this study, this is what will happen:
- ▪ After signing the consent form, you will fill out a brief survey that asks questions about your demographic information, medical history, obstetrical history, and family history.
- ▪ During your pregnancy, you will continue to see your obstetric provider and they will instruct you to take 81mg aspirin during your pregnancy until delivery following current standard of care guidelines for patients at risk for preeclampsia.
- ▪ At the time of delivery, you will be randomly assigned to one of two groups: the aspirin group or placebo group. Both groups will receive identical tablets and be instructed to take one tablet every night starting within 24 hours from birth up to 2 days postpartum and continue until 6 weeks postpartum. Those in the aspirin group will receive 81mg aspirin, and those in the placebo group will receive a placebo (a mixture of neutral substances without the addition of the active aspirin ingredient, designed to have no effect on the body) until 6 weeks postpartum. You will not know which group you have been randomized into since both tablets will look identical.
- ▪ You will have 5 in person study visits occurring at: 12-16 weeks’ gestation (initial visit for enrollment and consent), at the time of delivery (randomization), 1 week postpartum, 2 weeks postpartum, and 6 weeks postpartum. At these visits, we will measure your blood pressure, obtain blood and urine samples for analysis, review your medication compliance and dispense new medication to last until your next in person visit, and assess for any adverse effects related to the treatment.
- ▪ You will also have 1 telephone study visit occurring at: 4 weeks postpartum. During this call, we will assess for any adverse effects related to the treatment.
▪ You will be given a handheld tablet where you will complete a daily questionnaire that records any adverse effects that may be related to the treatment and document medication compliance.

▪ We will review your medical records for your pregnancy, delivery and for any hospital admission during the study period relating to your pregnancy and/or the study outcome. The data we will gather includes: gestational age at delivery, whether you developed antepartum preeclampsia or gestational hypertension, whether you delivered vaginally or had a c-section (and if so, why), any complications that may have occurred during labor and birth, assessment of your baby, reasons for admission to the hospital prior to delivery and/or in the postpartum period, tests procedures and/or medications administered during your hospital admission, and any medications you were discharged with.

▪ Your participation in this study will end after the final in person study visit at 6 weeks postpartum.

**What are the risks and discomforts of participating?**
We do not anticipate that any significant risks will occur in either study group related to the treatment. There are some general risks associated with the use of aspirin that are extremely small. These include abdominal pain, nausea, vomiting, heartburn, dizziness, headache, tachypnea, and bronchospasm. Rare but more serious risks include GI bleeding or hemorrhagic stroke. Participation in this study may involve risks that are not known.

**How will I know about new risks or important information about the study?**
We will tell you if we learn any new information that could change your mind about taking part in this study.

**How can the study possibly benefit me?**
We anticipate that women who receive low-dose aspirin during the postpartum period will have a lower risk of developing postpartum preeclampsia. This may help reduce the occurrence of adverse maternal outcomes such as postpartum eclampsia, stroke, and long-term cardiovascular complications.

**How can the study possibly benefit other people?**
The benefits to science and other people may include a better understanding of postpartum preeclampsia and how to prevent it.

**Are there any costs to participation?**
If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance.
Will I be paid for participation?
You will be compensated for taking part in this study. At the end of the study, you will receive a $25 gift card that can be used at any location.

What are my choices if I decide not to take part in this study?
Instead of participating in this study, you have some other choices. You could:
- Get treatment without being in a study. You can continue to see your obstetric provider.
- Take part in another study.

How will you keep my data safe and private?
We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person. We will keep information confidential by using only identification codes on study forms, storing any signed forms in locked cabinets, and using and storing data on a password protected computer that only specific research personnel will have access to.

We are committed to protecting the privacy of your health information. If you decide to be in this study, the researcher may get information that identifies your health information and may directly identify you, such as name, address, telephone number, and email address. At the earliest reasonable time, we will de-identify your information, meaning that we will replace the identifying information with a unique code that will be used for the rest of the study and does not directly identify you. The sub-investigator at your site will keep a link that identifies your coded information and you. Only the sub-investigator and specific research personnel will have access to this link. Any information that can identify you will be kept confidential. Your information and biospecimens collected as part of the research will not be used or distributed for further research studies. When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

What Information Will You Collect About Me in this Study?
The information we are asking to use and share is called “Protected Health Information.” It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:
- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
• The entire research record and any medical records held by MFMU Network and Yale University created from the time of study initiation until completion of all data analysis and reporting.
• Records about phone calls made as part of this research
• Records about your study visits
• Information obtained during this research regarding
  ▪ HIV / AIDS test results
  ▪ Hepatitis infection
  ▪ Sexually transmitted diseases
  ▪ Other reportable infectious diseases
  ▪ Physical exams
  ▪ Laboratory, x-ray, and other test results
  ▪ Diaries and questionnaires
  ▪ The diagnosis and treatment of a mental health condition
  ▪ Use of illegal drugs or the study of illegal behavior
  ▪ Records about any study drug you received
  ▪ Records about the study device

How will you use and share my information?
We will use your information to conduct the study described in this consent form. We may share your information with:
• The U.S. Department of Health and Human Services (DHHS) agencies
• Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
• The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
• The study sponsor or manufacturer of study drug/device
• Drug regulatory agencies in other countries
• Governmental agencies to whom certain diseases (reportable diseases) must be reported
• Health care providers who provide services to you in connection with this study.
• Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
• Principal Investigator of the study
• Co-Investigators and other investigators
• Study Coordinator and Members of the Research Team
• Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with
these individuals and/or companies that require that they keep your information confidential.

**Why must I sign this document?**
By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record. However, this is a double blinded treatment study and if you sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

**What if I change my mind?**
The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Katherine Kohari, MD at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

**What if I want to refuse or end participation before the study is over?**
Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. This may occur if you develop any serious adverse events and will be at the discretion of the sub-investigator at your clinical site.

**What will happen with my data if I stop participating?**
When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and
given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight

**Who should I contact if I have questions?**

Please feel free to ask about anything you don't understand.
If you have questions later or if you have a research-related problem, you can contact the Principal Investigator, Dr. Katherine Kohari.

If you have questions about your rights as a research participant, or you have complaints about this research, you can call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**Authorization and Permission**

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

<table>
<thead>
<tr>
<th>Participant Printed Name</th>
<th>Participant Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person Obtaining Consent Printed Name</td>
<td>Person Obtaining Consent Signature</td>
<td>Date</td>
</tr>
</tbody>
</table>
Appendix B: Recruitment Flyer
(will be translated into Spanish)

Volunteers Needed for a Research Study on Postpartum Preeclampsia.

If you are a pregnant woman between 12- and 16-weeks’ gestation, you may be eligible to participate in a research study involving the prevention of postpartum preeclampsia.

<table>
<thead>
<tr>
<th>You may be eligible to participate if</th>
<th>Participation involves</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ You are 18 years or older</td>
<td>▪ In person study visits scheduled at the same time as your regularly scheduled prenatal and postpartum visits, and telephone visits</td>
</tr>
<tr>
<td>▪ Have one of the following: history of preeclampsia, are pregnant for the first time, are pregnant with multiples, are currently diagnosed with hypertension, type 1 diabetes, and/or type 2 diabetes, have kidney disease, have an autoimmune disease, are over 35 years old, have a family history of preeclampsia, or have had an adverse pregnancy outcome previously</td>
<td>▪ All study related materials and procedures at no cost to you</td>
</tr>
<tr>
<td></td>
<td>▪ You will be reimbursed for your participation</td>
</tr>
</tbody>
</table>

Location: [Specific clinical site information here]

For more information or if you are unsure if you meet the requirements, please call or email a member of the study team:
[Name of site-specific contact and credentials]
[Position]
[Phone number]
[Email address]
Appendix C: Baseline Intake Survey
(will be translated into Spanish)

Participant Identification Code: __________  Date: ________  Age ______

*Please fill out this form to the best of your ability.*

1. Race
   a. White
   b. African American
   c. Asian
   d. American Indian or Alaska Native
   e. Pacific Islander

2. Ethnicity
   a. Hispanic or Latino
   b. Non-Hispanic

3. Current marital status
   a. Single
   b. Married
   c. Separated
   d. Divorced
   e. Widow

4. How many times have you been pregnant?
   a. 1
   b. 2
   c. 3 or more

5. How many prior live births have you had? (For pregnancies past 24 weeks’ gestation)
   a. 0
   b. 1
   c. 2
   d. 3 or more

6. How far along is your pregnancy? ________ weeks’ gestation

7. Has it been more than 10 years since your previous pregnancy?
   a. Yes
   b. No

8. Are you pregnant with multiples (twins, triplets, quadruplets, etc.)?
   a. Yes
   b. No
9. What was your pre-pregnancy weight? ________ lbs.

10. What is your height? _____ ft. _____ in.

11. Please indicate which medical condition(s) you have. Circle all that apply.
   a. Chronic hypertension
   b. Type 1 diabetes
   c. Type 2 diabetes
   d. Systemic lupus erythematosus
   e. Antiphospholipid syndrome
   f. Kidney disease

12. Have you ever given birth to a baby that had a low birthweight or was considered small for gestational age?
   a. Yes
   b. No

13. Have you ever been diagnosed with preeclampsia in a previous pregnancy?
   a. Yes
   b. No

14. Have you ever had any adverse pregnancy outcomes?
    a. Yes  If so, please indicate what type of outcome __________________________
    b. No

15. Has anyone in your family (mother or sister) been diagnosed with preeclampsia previously?
    a. Yes
    b. No

16. Do you currently use or have you previously used any statin medication?
    Examples include atorvastatin (Lipitor), lovastatin (Mevacor or Altoprev),
    fluvastatin (Lescol), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin
    (Zocor), and pitavastatin (Livalo).
    a. Yes
    b. No
Appendix D: Sample Daily Handheld Tablet Electronic Questionnaire
(will be translated into Spanish)

Participant Identification Code: 01234

Did you take your medication tonight?
- Yes
- No

Have you experienced any of the following today? Check all that apply.
- Hives
- Shortness of breath
- Lip swelling
- Facial redness
- Abdominal pain
- Nausea
- Vomiting
- Heartburn
- Headache
- Dizziness
- Blurriness of changes in vision
- Hyperventilation
- Other – please specify ______________________________
Appendix E: Telephone Visit Survey
(will be translated into Spanish)

*To be filled out by study coordinator during telephone visits with subject’s responses to the questions*

Participant Identification Code: __________

Have you been taking your medication daily? • Yes • No

How many tablets are left in the current opened bottle? _______

How many unopened bottles are left? _______

Have you experienced any of the following since your last visit? (Check all that apply.)
  • Hives
  • Shortness of breath
  • Lip swelling
  • Facial redness
  • Abdominal pain
  • Nausea
  • Vomiting
  • Heartburn
  • Headache
  • Dizziness
  • Blurriness or changes in vision
  • Hyperventilation
  • Other – please specify ____________________

Have you had to go to the hospital for any reason since your last visit? • Yes • No
If yes, why did you go and what happened? _____________________________________________
# Appendix F: Sample Size Calculation

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion Positive</th>
<th>N per Group</th>
<th>Standard Error</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin group</td>
<td>0.076</td>
<td>2,187</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>0.100</td>
<td>2,187</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate difference</td>
<td>-0.024</td>
<td>4,374</td>
<td>0.009</td>
<td>-0.041</td>
<td>-0.007</td>
</tr>
</tbody>
</table>

Alpha = 0.050, Tails = 2, Power = 80%

Adjusting for 10% attrition rate
4,374 x 0.100 = 437.4 = 438 needed in addition

4,374 + 438 = 4,812 total sample size (2,406 per group)


Tran S, Fogel J, Karrar S, Hong P. Comparison of process outcomes, clinical symptoms and laboratory values between patients with antepartum preeclampsia, antepartum with persistent postpartum preeclampsia, and new onset postpartum preeclampsia. *J Gynecol Obstet Hum Reprod.* 2020;49(5):101724.


