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Aspirin vs. Pravastatin for Prevention of Preterm Delivery in Patients at Risk for Pre-Eclampsia

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by

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Abstract

This literature review is an examination of the use of low-dose aspirin therapy versus the use of pravastatin therapy to prevent preterm delivery in women at risk of developing preeclampsia. Preeclampsia is defined as new onset hypertension after 20 weeks of gestation with evidence of maternal organ or uteroplacental dysfunction or proteinuria. Preeclampsia is a serious condition that affects pregnant women and their growing fetuses which may lead to maternal or fetal demise. The Prevention of preeclampsia with the use of low-dose aspirin in the first 12-16 weeks is currently the mainstay of treatment for women with moderate to severe risk factors predisposing them to develop preeclampsia. This literature review looks at the use of low-dose aspirin therapy to prevent preterm delivery and the potential side effects of this therapy on the mother and fetus. Additionally, this review provides some insight into new clinical trials using HMG-CoA reductase inhibitors, specifically pravastatin, and the risk and benefits of this potential treatment option.

Keywords: aspirin, pravastatin, preeclampsia prevention, preterm delivery,

Introduction

High blood pressure during pregnancy has remained a major concern and continues to put many mothers and unborn fetuses at risk. According to the Centers for Disease Control, pregnant individuals between the ages of 20-44 have a 1 in 12-17 odds of developing complications associated with increased blood pressure during pregnancy. High blood pressure during pregnancy is becoming increasingly common and remains a large issue during pregnancy. Complications of high blood pressure in pregnancy include chronic hypertension, gestational hypertension, and preeclampsia, which can progress to eclampsia, and then stroke. Complications are not just noted in the mother but also can affect the fetus, such as a decrease in blood flow to the placenta, placental abruption, intrauterine growth restrictions, and premature delivery.

The National Institutes of Health (NIH) compiled a list of risk factors that increase a woman's chances of developing preeclampsia while pregnant. The list includes women who have a history of previous preeclampsia, women with chronic high blood pressure or kidney disease, obesity, multiple gestations, and certain disorders such as lupus, scleroderma, and rheumatoid arthritis. A study published by Fox et al. (2019) revealed that hypertensive disorders affect up to 10% of pregnancies worldwide and of these pregnancies, three to five percent are complicated by preeclampsia. This study also included classifications that put women at higher risk of developing preeclampsia and includes many of the same criteria as listed above by the NIH

including women with a history of hypertensive disease during a previous pregnancy or a maternal disease including chronic kidney disease, autoimmune diseases, diabetes, or chronic hypertension. Moderate risk factors for women include being greater than 40 years of age, having a BMI greater than 35 kg/m, having a family history of preeclampsia, having a multi-gestational pregnancy, or having greater than 10 years since their last pregnancy.

Women who are in these moderate to high-risk categories as stated above are started on aspirin therapy between 12-16 weeks of gestation and are continued on this therapy until delivery. Aspirin therapy is utilized to reduce the risk of developing preeclampsia and its side effects. The last few years have shown that aspirin therapy has been the gold standard for preeclampsia prevention with little to no research studies or clinical trials done on other medications to prevent this common pregnancy complication. Moreover, pregnancy comes with a risk of its own so it is hard to justify studying medications that could have adverse effects on the mother or fetus. Currently, low-dose aspirin therapy has been one of the few studied drugs for preeclampsia prevention however HMG-CoA reductase inhibitors have shown some promising results. Specifically, pravastatin has been in two clinical trials over the last 5 years that have been working to prove that it is a safe medication for use in pregnancy and it has the potential to prevent preeclampsia and preterm delivery.

The importance of this study is to look at women's health and pregnancy to provide the best and safest option to prevent preeclampsia and reduce the incidence of preterm delivery. The health of women during pregnancy offers a unique challenge as providers are trying to manage the mother's health conditions while also managing the fetus. This literature review focuses on retrospective cohort studies, double-blinded studies, and clinical trials into account when comparing pravastatin and low-dose aspirin therapy and offering up evidence to support the

usage of these medications to prevent preterm delivery. While this literature review is used to look closer at the prevention of preeclampsia and preterm delivery, it also discusses other variables such as adverse effects on the growing fetus, bleeding risk in the mother, and additional information on pravastatin's effect on plasma levels in the placenta. The information in this literature review will not explore research associated with ethnic or racial groups and this set of information will only be referred to as appropriate in this study.

Statement of Problem

Preeclampsia and preterm delivery have continued to plague the healthcare system with no advancements in prevention and minimal improvements to guidelines in the last five years. The study has reviewed clinical trials of aspirin therapy and pravastatin therapy to compare their efficacy in preventing preeclampsia and preterm delivery. The literature reviewed also evaluates the safety of each medication when used during pregnancy and the associated adverse effects to maternal health and fetal health.

Research Question

In pregnant patients at risk of developing preeclampsia what drug management between aspirin and pravastatin is more effective at delaying preterm delivery?

Methods

A literature review was performed using different electronic databases such as PubMed, and Google Scholar. Additional information was gathered using professional associations like the American College of Obstetricians and Gynecologists (ACOG) to find articles related to the topic of aspirin and pravastatin use in pregnancy. *Keywords* were used to establish literature sets discussing the use of aspirin and pravastatin in preventing preeclampsia and their ability to decrease the incidence of preterm labor, they included aspirin to prevent preeclampsia,

pravastatin to prevent preeclampsia, risk of aspirin in pregnancy, risk of pravastatin in pregnancy, and safety of each drug with relation to pregnancy. While using PubMed and upon reviewing different research articles, a number were selected via "The Similar" articles and Reference list for this literature review. All searches were narrowed to the past 5 years with one exception from the past 15 years that was used to review congenital anomalies associated with statin use. All studies that were not in English were excluded, systemic reviews were excluded, and many studies were excluded as they included more variables such as race and ethnicity that were not as easily comparable among other studies. A total of 7 studies were left after all exclusion criteria were met.

Literature Review

Risk reduction of preterm preeclampsia and preterm delivery with pravastatin prophylaxis

Costantine, et al. (2021) performed a multicenter, blinded, placebo-controlled randomized trial of 20 women of varying race and ethnicity (White, Black, Asian, Hispanic, and non-Hispanic) with singleton, nonanomalous pregnancies at high risk for preeclampsia. This study aimed to support the safety and utility of pravastatin for the prevention of preeclampsia. Participants eligible for this study had to be 18 years or older to participate. This study focused on women between 12 +0 weeks of gestation and 16+6 weeks of gestation measured by ultrasound, these women all had a history of preeclampsia with severe features in a previous pregnancy that required delivery before 34+6 weeks. The exclusion criteria for the study included pregnancy with known fetal genetic or major malformation; fetal demise; multifetal gestation; those with contraindications for statin therapy; statin use in current pregnancy; concomitant therapy with fibrates, niacin, cyclosporine, clarithromycin, or erythromycin, HIV infection; history of solid organ transplant; chronic renal disease; uterine malformations, cancer,

or participation in another intervention study that could influence the outcome. This study was approved by the FDA as an investigational new drug study.

Before the randomization of participants, all patients were documented to have normal liver transaminase levels. Ten women were then randomly selected to participate in each group, via a central process that was prepared and maintained at the University of Texas Medical Branch's Investigational Drug services, to receive either a daily dose of 20 mg of pravastatin or a placebo that was packaged and given to each participant. The prepackaged medications were manufactured by the University of Iowa to be identical capsules. Patients were instructed to take one capsule daily until delivery or until any condition developed that would require them to discontinue the assigned capsule. All participants such as the patients, primary care providers, investigators, and outcome assessors were blinded during the trial and analysis. Research personnel continued to follow patients at scheduled intervals and oversee that patient care and care of the fetus were all according to standard practice. Medication side effects were assessed at each visit using a checklist, adverse events were determined and assessed, and pill count was performed to ensure adequate compliance. The treatment of the patient's pregnancy was left to the discretion of the treating physician and was performed as recommended by standard prenatal care as defined by the participating institution.

Pharmacokinetic studies were performed and conducted in the second and third trimesters, and then at postpartum. The time periods assessed were between 18-24 weeks, 30-34 weeks, and then 4-6 months postpartum. Patients stopped their study capsule right at the time of delivery and then restarted 4 days before their 4-6 month postpartum appointment. Patients were in control of their medication at this time and medication adherence was measured by the pill count on the day of the appointment.

The results concluded that common side effects were headache, heartburn, and musculoskeletal pain, no one reported any incidence of rhabdomyolysis or liver injury, however, one patient did develop muscle weakness, but this stopped after the drug was discontinued. There were two congenital anomalies that occurred in the placebo group to include atrial septal defect and hypospadias, none of these effects were noted in the pravastatin group. The pravastatin and placebo group had no outcomes of maternal, fetal, or infant death. The pharmacokinetics showed no significant difference during the second and third trimesters and there was a limited number of test subjects, so data compared during pregnancy and postpartum were not conducted. Maternal and neonatal outcomes showed that 2 out of 10 participants in the pravastatin group developed preeclampsia with severe features vs. 5 out of 10 in the placebo group developing preeclampsia with severe features. Three out of ten participants had preterm deliveries (before 37 weeks gestations) in the pravastatin group vs. 6 out of 10 in the placebo group. Most neonatal and obstetrical outcomes were similar between the 2 groups and all newborns passed their auditory brainstem response evaluation. The concentration of maternal angiogenic biomarkers and cholesterol concentrations, umbilical cord blood biomarkers, enzymes, and hormones did not show any difference when comparing the two groups. None of the data comparing these two groups in terms of side effects and characteristics showed any statistical significance with a p-value above 0.05, the only statistically significant piece of data was shown to be in renal clearance and net renal secretion clearance of pravastatin in the second and third trimester compared to 4-6 months postpartum. This rendered a p-value of less than 0.05 making the data statistically significant. This piece of information is important because it shows that clearance, half-life, and time to reach maximum concentrations of pravastatin were equal in pregnant

individuals and non-pregnant individuals showing that the fetus is not at any increased risk of adverse effects of the drug in the system.

While this study is small and pharmacokinetics were hard to measure with this cohort size, there is minimal evidence proving that pravastatin is not harmful to the fetus or mother. It is noted that the exact mechanism of pravastatin action is unknown but there is thought that it can reverse specific angiogenic imbalances and any oxidative and inflammatory stress and restore global endothelial health in pregnancy. However, this study was not well equipped to measure this outcome. The strengths and limitations of this study are the fact that this is only a second pilot study with strict safety measures provided by the FDA which limited the sample size, this sample size could have made it easier for the groups unbalanced with different associated biased after the randomization. This sample size also limited the pharmacokinetic study of the postpartum group as not all individuals participated in this portion of the study.

Another study focusing on pravastatin was performed by Ahmed et al. (2019). This study was a double-blind multicenter, placebo-controlled randomized trial called StAmP (Statins to Ameliorate Pre-Eclampsia). The trial took place in 15 maternity units across the UK with each participant providing written informed consent before randomization. The object of this study was to determine whether statins could reduce soluble fms-like tyrosine kinase-1 (sFlt-1) as supported in pregnant animals with pre-eclamptic-like symptoms. This study focused primarily on the effects of pravastatin on plasma sFlt-1 levels during pregnancy complicated by preeclampsia.

Women over the age of 18, who presented with preeclampsia between 24+0 through 31+6-weeks' gestation, with a single viable fetus and no major anomalies were eligible to be included in this randomization study. The study included women of white, mixed, Asian, Black,

and Chinese ethnicity along with current smokers, non smokers, and women who quit smoking when they found out they were pregnant, in total the study included 62 women. The definition of preeclampsia for this study included new-onset hypertension with diastolic blood pressure greater than 90 and new onset two plus protein found on the urinary dipstick, with confirmatory protein that was defined as creatinine ratio greater than 30mg/mmol or greater than 300 mg total protein in a 24-hour urine sample. The study also included women with chronic hypertension that had superimposed preeclampsia. The exclusion criteria for this study centered around whether the attending clinician considered the pregnancy unlikely to continue for more than 48 hours after preeclamptic diagnosis, women already taking statins, or women that had contraindications for taking statins.

The randomization of the study was done by the University of Birmingham Clinical Trials Unit which separated all eligible consenting women in a 1:1 ratio by a secure telephone or web-based central randomization service. The number associated with the drug packs was not revealed until each woman who had committed to the trial was confirmed to have met eligibility criteria. The packs were randomized so each woman either received daily pravastatin (40mg) or a placebo of identical appearance. The drug provided to the women was dosed orally each evening until childbirth. These women were expected to remain as inpatients in their respective hospitals but were allowed to be treated as an outpatient if their condition was stable and they could be managed as such. Computerization was used to achieve some balance between the groups to account for gestational age at diagnosis, smoking status, and severity of hypertension.

The primary maternal outcome was the mean maternal serum sFlt-1 levels during the first 3 days post-randomization. Secondary anti-angiogenic outcomes were serum concentration of sFlt-1 and the sFlt-1: P1GF ratio over the first 14 days after randomization and during the

remainder of the pregnancy. The main secondary outcome studied was the time from randomization to the time of childbirth. They also considered the indicators for preeclamptic severity which included blood pressure, proteinuria, serum levels of creatinine, uric acid, albumin, liver transaminase, electrolytes, platelets, and those of maternal status were prothrombin time, C-reactive protein, hemoglobin, and bilirubin. Fetal well-being continued to be assessed using cardiotocography, umbilical artery blood flow, and amniotic fluid volume. Blood and urine samples were measured and assessed using routine assays, daily for 3 days post-randomization, twice a week until the mother was discharged from the hospital postpartum, and then 6 weeks postpartum. Soluble Flt-1 and P1GF were measured in a single batch analysis using the BRAHMS Kryptor system.

The neonatal outcomes that were measured included birthweight, Apgar scores at 1 and 5 minutes, and the incidence of neonatal complications and prematurity were assessed. When possible, a paired collection of maternal and umbilical cord blood samples at birth was collected for central batch quantification of pravastatin and pravastatin lactone using a Shimadzu Nexera XR HPLC analyzer. Any adverse effects were reported by participating clinicians and reviewed by the data monitoring committee. They were considered serious adverse reactions if they resulted in maternal or fetal death or threatened the life of the mother or baby, resulted in longer than anticipated postnatal maternal admission and were considered causally related to the study treatment, and were classed as unexpected if not within the known side effect profile of pravastatin. The management of women with preeclampsia was directed by the UK guidelines for the management of hypertension in pregnancy and was left to the judgment of individual clinicians. The drivers for childbirth included uncontrollable hypertension, worsening maternal

blood profile, a non-reassuring cardiotocograph, and reversed end diastolic flow in the umbilical artery.

When the study concluded there was no maternal death and all 30 infants born to mothers who received pravastatin survived, however, only 29 of the 32 infants from the women who received the placebo survived. Pravastatin showed to prolong the pre-eclamptic pregnancy compared with the placebo but this comparison was proven to be insignificant with a p=0.6. Maternal plasma levels of sF1t-1 were lower in the pravastatin group compared with the placebo group, the difference was small and not statistically different over days 1-3 (292pg/ml, 95% CI-1175 to 592; p=0.5) and days 1-14 (48pg/ml,95% CI -1009 to 913; p=0.9) There were no differences found between groups for maternal plasma P1GF levels nor for the sF1t-1 ratio and no difference in the sF1t-1 or S1t-1:P1GF ratio in the postpartum group. Maternal blood pressure and all biochemical parameters remained similar between both groups over the first 3 days and up to day 14. Additionally, markers for fetal growth and well-being, including umbilical artery pulsatility index, did not differ between the two groups. The surviving infants shared similar birth weights, Apgar scores, and adverse outcomes associated with prematurity were similar. The overall outcome of the study showed little difference between the pravastatin group and the placebo group.

A few limitations to this study include the number of participants at only 62 compared with the larger numbers involved in the aspirin studies researched below. The number of participants was limited in this study because of the increase in early onset preeclampsia, rapid clinical deterioration, and the inability to gain informed consent before starting the trial. Pravastatin is still contraindicated in pregnancy which was also a deterrent in the number of participants. Unfortunately, the compliance of each drug group was lower than expected even

with the inpatient management further skewing data. The study could have also been impacted by the timing of cord blood venesection as it was not always consistently measured. The outcome of the study could have changed if the measurement was done on a timed relation to the last dose of pravastatin given to the participant and could have further helped to distinguish why the drug concentration was at the lower limits of normal when detection was done with the assay. Further research could investigate the time that pravastatin was started to show a better comparison to aspirin therapy.

Risk reductions of preterm preeclampsia and preterm delivery with aspirin prophylaxis.

Hoffman et al. (2020) conducted a multinational, randomized multi-country (Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, Zambia) double-masked, placebo-controlled trial of daily 81mg of aspirin vs. daily placebo initiated between 6+0weeks gestation and 13+6weeks gestation to determine if initiation of aspirin therapy before 16 weeks could reduce the risk of preeclampsia and incidence of preterm birth before 37 weeks. The study aimed to prospectively assess the potential maternal/neonatal safety of aspirin use in limited resource settings. The trial was conducted by the NICHD Global Network for Women's and Children's Health Research in 7 sites in 6 countries between March 2016 and April 2019. Nulliparous pregnant women between the ages of 14 (18 when required by individual ethics boards) and 40 years of age were identified and individually consented to participation by trained staff. All women were required to be pregnant between 6+0 weeks or 13+6 weeks, this confirmation was performed by ultrasound. Women were excluded if they had a medical history that included allergy or contraindication to aspirin; if they had previously taken aspirin for more than 7 days during this pregnancy; if their pregnancy was multiple gestational; if there was a history of more than two first trimester losses; or if they had medical conditions for which low-dose aspirin

therapy is currently indicated (diabetes and hypertension). All potential participants then underwent a medical screening and were required to meet the following criteria before participation was allowed, blood pressure below 140/90; hemoglobin at or above 7.0 g/dl; and an ultrasound evaluation with the presence of a fetal heartbeat, single gestation, and absence of fetal anomaly. The crown-rump length and last menstrual period were entered into a smartphone application to determine the gestational age in accordance with ACOG guidance.

Consenting and eligible women were randomly assigned in a 1:1 ratio to receive a regime of either 81mg aspirin daily or a placebo. Manufacturing of the aspirin tablet and placebo tablets was by Morepen Laboratories in Parwanoo, Himachal Pradesh, India, and Helix Pharma Limited located in Karachi, Pakistan. The packaging and distribution were handled by Bilcare Research Global Clinical Supplies. The placebo tablets were manufactured to be identical to the aspirin tablets in terms of size, weight, and appearance. Each set of pills, aspirin or placebo was packaged into blister cards containing a 2-week supply of medication. Certificates of analysis following the United States pharmacopeia reference standards were performed. Stability testing was also done at 6, 12, 18, and 24 months for each lot, this was performed by high-performance liquid chromatography for active ingredients and appearance by RTI International. The randomization sequence for each site was developed by the data coordination center (RTI) using a computer algorithm based on a randomly permuted block design with varied block sizes. Blister packs were exchanged every 2 weeks by study personnel from centrally maintained storage facilities, and an assessment to determine compliance, side effects, interval medical contacts, and concomitant medications were documented. Local healthcare providers and research staff were blinded to treatment to keep more confidentiality. Blood pressure assessments were made between 16 to 20 weeks, 28 to 30 weeks, and then biweekly beginning at

34 weeks until delivery. Hemoglobin assessments were obtained between 26-30weeks. Maternal and neonatal outcomes were obtained over 42 days.

The primary outcome of this study was to assess preterm birth, which was defined as any delivery at or after 20 weeks gestation and prior to 37 weeks' gestation. Predefined secondary maternal outcomes were hypertensive disorders of pregnancy, early preterm (before 34 weeks gestation) hypertensive disorders of pregnancy, vaginal bleeding, antepartum hemorrhage, postpartum hemorrhage, maternal mortality through 42 days postpartum, and late abortion. Predefined secondary fetal/neonatal outcomes were perinatal mortality, early preterm birth (before 34 weeks), small for gestational age defined by the Intergrowth standard, birth weight less than 1500g, birthweight less than 2500g, spontaneous abortion, stillbirth, fetal loss, or medical termination of pregnancy. The primary outcome was estimated to be 8%, assuming that 5% would have a risk of miscarriage and 2% would be lost to follow-up. The sample size wanted was 11920 participants with half of the participants going to either aspirin or placebo, this would allow for a 90% power to detect a 20% reduction in the incidence of preterm birth in women treated with low-dose aspirin therapy, assuming the two-sided type one error was 5%.

A total of 14361 participants provided informed consent between March 2016 and June 2018, a total of 2385 women were excluded or declined randomization, and the remaining 11976 were consented and randomized. The number of participants assigned to low-dose aspirin therapy were 5990 and 5986 were assigned to the placebo. Of the 5990 women assigned to the aspirin group, 5787 were in the modified intent to treat (MITT) population and the placebo group contained 5771. Overall adherence to the medication or placebo was defined as taking greater than 90% of the medication prescribed, this was considered high adherence. The MITT population's overall adherence was 84.9%: aspirin was 85.3% and placebo was 84.4%. The

primary outcome of the study measuring preterm delivery, or delivery before 37 weeks, occurred in 11.6% of women receiving aspirin therapy and 13.1% of women in the placebo group (RR, 0.89; 95% CI, 0.81 to 0.98; RD,-0.02; 95%CI, -0.03, -0.01) with a p=0.012 which is statistically significant and shows that aspirin therapy can reduce preterm delivery.

Secondary outcomes such as early preterm delivery, or delivery before 34 weeks, were reduced in women who were taking aspirin compared to those taking the placebo, this trend continued for extremely preterm deliveries, defined as deliveries before 28 weeks. Perinatal mortality was shown to occur less frequently among women who were randomized to aspirin compared to placebo, 45.7/1000 vs. 53.6/1000. It was shown that hypertensive disorders of pregnancy did not seem to differ between groups however the incidence of women who were delivered before 34 weeks with hypertensive disorders of pregnancy was lower in women taking the aspirin vs. placebo, and this proved to be statistically significant (p=0.015). This further strengthens the argument that aspirin therapy is helpful when used before and after hypertensive symptoms arise. Another statistically significant data point with a p value=0.039 included the incidence of fetal loss defined as infant death after 16 weeks gestation and before 7 days postpartum, which was lowered among women who were taking aspirin. The overall risk of serious adverse events was similar in each group. There was no difference in maternal bleeding complications among the aspirin group or placebo group. There was also no difference in the incidence of serious fetal/neonatal adverse events between the aspirin and placebo groups.

It was concluded in this trial that administration of 81mg of aspirin beginning between 6 weeks and 13+6 weeks through 36 weeks resulted in a lower incidence of preterm birth amongst women with a singleton pregnancy in low and middle-income countries. This study was double-blind which improves the overall strength of the study and provides good information with less

bias attached, it was noted at the end of the study that no authors of the study had any interest to declare, which shows little bias. The N value of the study was larger than some of the other comparison studies above. There was data that proved to be statistically significant in this data set and showed strong evidence that aspirin therapy is effective. The primary focus of this trial was set in low to middle-income countries which makes it difficult to ascertain the applicability to practice in the United States.

Rolnik et al. (2017) performed a multicenter, double-blind, placebo-controlled study to determine if low-dose aspirin intake during pregnancy reduces the risk of preterm preeclampsia. The design of this study was used to compare 150 mg of aspirin per day vs placebo, both were administered from 11 to14 weeks of gestation until 36 weeks of gestation in women with singleton pregnancies who were at high risk for preterm preeclampsia. Thirteen hospitals were involved in this clinical trial and included hospitals in the UK, Spain, Italy, Belgium, Greece, and Israel. Any woman that came for a prenatal exam at one of the participating facilities between 11+0weeks of gestation to 13 +6weeks of gestation was offered to screen for preeclampsia using an algorithm that combines maternal factors, mean arterial pressure, uterine artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor. The gestational age was determined from the measurement of fetal crown-rump length. Maternal characteristics such as height and weight were recorded along with medical and obstetrical histories. The mean arterial pressure was measured by validated automated devices with the use of a standardized protocol. The average value was recorded from the transabdominal color doppler ultrasonography by measuring the left and right uterine artery pulsatility index. PAPP-A and P1GF1-2-3 kits and DELFIA Xpress random access platform, PerkinElmer, were used to measure the serum concentrations of pregnancy-associated plasma protein A and placental

growth factors. University College of London Comprehensive Clinical Trials Unit was used to monitor quality control and screening to verify adherence to the protocol put forth by the trial.

Women over the age of 18 years with a singleton pregnancy; a live fetus between 11 to 13 weeks; and high-risk factors according to the screening algorithm that predisposed them to preeclampsia, were able to participate in the clinical trial. Exclusion criteria for the study included unconscious or severely ill status, learning difficulties or serious mental illness, major fetal abnormality identified at the time of scanning, regular treatment with aspirin 28 days before screening, bleeding disorders such as von Willebrand's disease, peptic ulceration, hypersensitivity to aspirin, long-term use of NSAID medication, and participation in another drug trial within 28 days before screening. Written informed consent was required from all trial participants. Randomization of eligible women was assigned in a 1:1 ratio using a Web-based system (Sealed Envelope), which chose whether the eligible women received either aspirin therapy or placebo therapy. The aspirin and placebo tablets were manufactured by Actavis UK and were packaged, labeled, stored, and distributed by Mawdsley-Brooks. To make the tablets identical, variables such as size, thickness, physical properties, and appearance were taken into consideration to make the placebo the same as the aspirin. After the randomization had occurred each participant was prescribed a single nightly dose of either aspirin or placebo for the duration of the trial. Each participant was then instructed to stop the tablet at 36 weeks gestation, or in the event of early delivery, at the onset of labor. The primary outcome that was measured was delivery with preeclampsia before 37 weeks of gestation. Secondary outcomes were adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation, stillbirth or neonatal death, death and neonatal complications, neonatal therapy, and poor fetal growth (birth weight below the 3rd, 5th, or 10th percentile). The

sample size of the study assumed that first-trimester screening would be able to detect 76% of the cases of preterm preeclampsia at the screen-positive rate of 10%. The team hypothesized that low-dose aspirin would result in a rate of preterm preeclampsia that was 50% lower than the rate with the placebo, for an estimated rate of 7.6% in placebo and 3.8% in aspirin. The enrollment was then calculated to be 1600 participants to give the trial 90% power to show a treatment effect at a two-sided alpha level of 5%. After accounting for attrition, the target recruitment became 1776.

Adherence was assessed by counting the tablets that each participant returned at each visit and by telephone interviews where the participants reported their own number of tablets. Adherence was good if the reported intake of tablets was 85% or more of the total number that each participant was expected to have taken between the date of randomization and the date of the visit at 36 weeks gestation or the date of delivery if delivery occurred before 36 weeks. Adherence was moderate if the intake was between 50% and 84.9% and considered poor if adherence was less than 50%. Adherence and adverse events were assessed at follow-up clinical visits at 19 to 24 weeks of gestation, 32 to 34 weeks gestation, and through three telephone interviews that occurred at 16 weeks, 28 weeks, and 30 days after the last tablet was taken. Side effects and adverse events were encouraged to be written down in diaries by each participant to be reviewed at each trial visit and each telephone interview. Researchers were instructed to ask about adverse events and side effects at each visit and telephone interview.

The trial first started in April 2014 at King's College Hospital in the UK and was stopped in June 2014 because of administrative problems with the supply of trial products. The women who were enrolled during this period were still included in the trial population as the manufacture and composition of the products remained the same throughout the trial. The trial

was restarted in July 2015, and recruitment was completed in April 2016. There was a total of 26,941 women with singleton pregnancies that had undergone screening, of these 2971 (11%) were found to be at high risk for developing preterm preeclampsia. However, 322(11.2%) were excluded from the trial as they did not fit into the eligibility criteria. Of the 2641 women eligible, 1776 (67.2%) agreed to participate and after randomization 152(8.6%) withdrew consent. At the end of the trial, 4 of the women who participated were lost to follow-up. The difference between the aspirin group and the placebo group was insignificant regarding the characteristics of the participants at baseline. The aspirin group had 11 miscarriages before 24 weeks of gestation, two pregnancy terminations for fetal abnormalities at or before 24 weeks of gestation, one pregnancy termination for severe fetal growth restriction and preeclampsia at 24 weeks of gestation, seven stillbirths at or after 24 weeks gestation, one neonatal death within 28 days after birth, and 776 live births of infants who survived until discharge from the hospital. The placebo group had 12 miscarriages before 24 weeks gestation, four pregnancy terminations for fetal abnormalities at or before 24 weeks gestation, no pregnancy terminations for severe fetal growth restrictions, 12 stillbirths at or after 24 weeks of gestation, two neonatal deaths within 28 days after birth, 792 live births of infants who survived to discharge from the hospital. In the aspirin group, Preterm preeclampsia occurred in 13 of 798 participants (1.6%), as compared with 35 of 822 (4.3%) in the placebo group, with an adjusted odds ratio in the aspirin group, 0.38; 95% CI, 0.20 to 0.74; p=0.004). Of the 152 women that withdrew from the trial, 78 had allowed their data to be reported, the characteristics of the women who withdrew consent were similar to those assigned to receive aspirin and those assigned to receive a placebo, and an analysis was performed to evaluate the effect of the withdrawals and showed no substantive difference from the primary analysis. Of the participants in the aspirin group, one serious adverse event occurred in 13

participants (1.6%) and at least one adverse event occurred in 207 participants (25.9%). Compared to the placebo group, 26 participants (3.2%) experienced one serious adverse event and 210 participants (25.5%) experienced at least one adverse effect.

This trial was able to conclude that 150mg of aspirin administered from 11 to 14 weeks of gestation until 36 weeks of gestation was able to significantly lower the incidence of preterm preeclampsia over a placebo. However, this trial was not able to conclude that other incidences of pregnancy complications or adverse fetal or neonatal outcomes were affected by the initiation of aspirin therapy starting at 11 to 14 weeks. This trial did not show any ability of aspirin to reduce the incidence of term preeclampsia in pregnancy. The study provided good data and was performed as a double-blind study which increases its strength. The total number of participants is larger than in studies used to compare pravastatin medication and placebo. However, this study also takes place outside of the United States which makes the information not as applicable to the healthcare system here,

The risk of statin therapy and aspirin therapy during pregnancy

Chang et al. (2021) performed a retrospective cohort study that included 1,443,657 pregnant women ages 18 or older that had their first infant born between January 1, 2004, to December 31st, 2014. This data was compromised and taken from the Taiwan National Health Insurance Research Database with a statistical analysis performed from April 7th, 2020, to July 31, 2021. This study was introduced to analyze the risk and adverse outcomes of statin use during pregnancy. The study excluded participants that were younger than 18, anyone with multiple pregnancies, any women with epilepsy, or those who used teratogenic drugs during pregnancy. The final population of the study was 1,371,356 parturient women, with 22, 576 of them being women that had been previously exposed to statins. 22,104 women were excluded

from this study for having no exposure to statins during pregnancy, three more women were excluded because of exposure to both lipophilic and hydrophilic statins. This left the study with a total of 469 women, who were prescribed statins during their pregnancy, to be analyzed. The indication for statin prescription, according to Taiwan FDA guidelines was dyslipidemia, therefore this study followed women who had a diagnosis of dyslipidemia. These women were further categorized according to maternal age and the year their children were delivered. The use of statin therapy was distinguished by a prescription being filled and used for at least seven consecutive days. The use of statin medication was further categorized to include lipophilic and hydrophilic statins. Pravastatin, a hydrophilic statin was used in a total of eight participants.

Certain characteristics including maternal age, and comorbidities prior to pregnancy, were analyzed and hypertensive disorders were recorded. Hypertension and diabetes were diagnosed before pregnancy, with diabetes being based on a random blood glucose level over 200 mg/dL or more, a fasting glucose of 126 mg/dL or more, or a hemoglobin A1c level of 6.5% or more. Hypertension was diagnosed with two to three office visit BPs greater than 140/90 mm Hg or more. The primary study was focused on outcomes that included congenital malformations, which were based on the diagnosis of 1 or more organ-specific malformations. Secondary outcomes were also reported which included birth weight, gestational age, preterm birth, low birth weight (less than 2500g), very low birth weight (less than 1500g), fetal distress, and Apgar scores at 1 minute and 5 minutes.

The statistical analysis performed from April 7th, 2020 to July 31^{st,} 2021 showed continuous variables measured with standard deviation (SD) values and categorical variables shown with percentages. The risk ratio for congenital anomalies, preterm birth, low birth weight, very low birth weight, Apgar score at 1 minute and 5 minutes, and fetal distress associated with

statin use was estimated by a Poisson regression model with robust error variance. All data was analyzed using SAS, version 9.4 software and all p values were from 2-sided tests, and results were deemed statistically significant at $p<0.05$. This study had a total of 469 women who were 18 years or older that were primiparous mothers who used statin therapy during pregnancy and 4690 that did not have any exposure to statin therapy during pregnancy. Diabetes and hypertension proved to be significantly higher in the statin-exposed group of women, which could be the reason that statin therapy was initiated. The gestational age at delivery was 38.4 weeks in the statin-exposed group and 37.3 in the unexposed group. The SD for birth weight was 444.3g in the statin-exposed group and 684.1g for the statin-unexposed group. The study analysis also showed that mothers exposed to statin therapy had a greater risk of developing preeclampsia or eclampsia and their infants were at increased risk of being born early and having lower 1-minute Apgar scores. This data was further broken down to distinguish the risk associated with pregestational diabetes. Pregestational diabetes increased the risk of congenital anomalies, but this was not associated with statin exposure. Women without diabetes or hypertension that were on a statin still experience preterm delivery. The statin exposure was further broken down into lipophilic and hydrophilic categories and this showed an increase in preterm birth, however, only lipophilic statin exposure was associated with low birth weight and only hydrophilic was associated with low 1minute Apgar scores.

This study was conducted to look at the risk of statin use during pregnancy and its thought to cause congenital anomalies in pregnancy. Statins have long been categorized as teratogenic during pregnancy and have been contraindicated, however, this data suggests that it may be a safe medication to use if needed during pregnancy. The study emphasized that inappropriate drug use during pregnancy should be avoided and because of this ethical

conundrum it is hard to research new drugs for safety and efficacy in pregnant populations. The conclusion of this study as stated suggests that statins may be safe to use during pregnancy, but larger studies have not been able to prove or disprove this assumption.

This study was a retrospective which could lead to missing data that could have further helped add to the results and conclusions of this study. However, this study had a larger number of participants than most of the available statin studies, which led to more available data, it was also double-blinded and had a wide variety of participants. There were no biases associated with the studies that are listed and outcomes were measured straightforwardly. The secondary outcomes of the study were not easily measured and therefore data was not found to be significant because the study design did not focus on these outcomes. Overall, the study was able to answer the research question with strong data and a decent number of participants.

Another study used to focus on the use of statin therapy and its adverse effects was done by Ofori et al. (2007). The population-based pregnancy registry was used to examine the association between the use of statin therapy in early pregnancy and the incidence of congenital anomalies. The study started out by sharing physiological increases in serum lipid concentrations that bodies naturally go through during pregnancy, this included triglyceride levels increased by 300-400% in the third trimester and cholesterol levels rising 25-90% higher than in a nonpregnant state. Current recommendations suggest that women discontinue statin use if they plan to become pregnant and some recommendation state that women of childbearing years should not be on a statin at all. Prior to this study, no controlled studies had been done to assess teratogenic potentials of statin drugs in humans.

Three administrative databases of the Province of Quebec: the Regie de l'assurance Maldie du Quebec (RAMQ), Med-Echo, and the fichier des evenements demographiques du Quebec (birth and death registries) of l'Institue de la Statistique du Quebec (ISQ) were used to establish data for this study. These three databases, RAMQ, Med-Echo, and ISQ were linked together and created the 'Medication and Pregnancy' registry. This registry contained data on all pregnancies that occurred in Quebec between January 1st 1997- June 30th, 2003. This registry particularly focused on women with a diagnosis or procedure code related to pregnancy that was identified by the RAMQ or Med-Echo database. The women eligible for the 'Medication and Pregnancy' registry were women that were between the ages of 15 and 45 on the first day of gestation, they had to be continuously insured by the RAMQ drug plan for 12 months before the first day of gestation and the duration of their pregnancy, and they had to have filled a prescription for a statin or fibrate or nicotinic acid in the year before or during their pregnancy. The specific drugs studied were those reimbursed by the RAMQ when this study took place. They included the following statins: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Women were excluded from the registry if they had filled a prescription for a category X drug such as carbamazepine, phenytoin, valproic acid, lithium, acitretin, isotretinoin, antineoplastic agents, leflunomide, and androgens. Three study groups were defined and were as follows; Group A was defined as women who had filled prescriptions for statins only before and during the first trimester of pregnancy, but who did not use fibrates or nicotinic acid; Group B included women who had filled prescriptions for fibrates or nicotinic acid only, before and during the first trimester, but did not use statins; Group C included women who had filled prescriptions for statins only in the period between 1 year before conception and 1 month before conception, and who did not have any filled prescriptions for any antilipidemic medications in

the period between 1 month before conception and end of pregnancy. These individual groups were selected to better represent their clinical interests, those who stopped statins before pregnancy, those who continued their statins, and those who used nonstatin antilipidemic medications.

The 'Medication and Pregnancy' registry included 110,313 women and of these women 153 women received statin therapy during the first trimester of pregnancy (group A), 29 received fibrate or nicotinic acid in the first trimester of pregnancy (group B), and 106 women received a statin in the period between one year before conception and 1 month before conception (group C). The most filled prescription for statins in groups A and C were atorvastatin, pravastatin, and simvastatin. In all the cases of first-trimester statin or fibrate use, prescriptions were not renewed in the second trimester. The study performed a link of mother-baby date for 64/69 known live births for group A, 14/15 known live births for group B, and in group C all births were successfully linked to babies 67/67. The rate of congenital anomalies was 4.69% in group A, the rate in group B was 21.43%, and group C was 10.45%. the rest of the registry had a 6.97% rate of congenital anomalies to put the data into comparison. The most common anomalies detected were related to cardiac anomalies. In Group A these included ventricular septal defects and atrial septal defects, the statin medications associated with these anomalies included lovastatin, atorvastatin, and simvastatin. Although it was used in about 20% of the first-trimester participants, pravastatin showed no increase in congenital anomalies. Group B had associated cardiac anomalies, one musculoskeletal anomaly, one case of tuberous sclerosis, and an anomaly of the eye. Group C was associated with musculoskeletal, limb, cardiac, and respiratory anomalies, which suggested no specific pattern in anomalies. In all three categories, it is noted that the participants were taking the standard recommended therapeutic dose.

The registry concluded that the overall incidence of congenital anomalies in pregnancies where prescriptions for statins had been filled in the first trimester of pregnancy was not statistically greater than the incidence in those pregnancies where prescriptions for fibrates only had been filled in the first trimester, or where the statins had been stopped at least 1 month before conception. There also was no evidence to a pattern in congenital anomalies among the live births. Weaknesses of this study include the small sample size with limited data on statin use during pregnancy for comparison. The study also mentioned a point about how live births were studied while adverse outcomes can also occur in the womb leading to fetal demise potentially associated with drug use. Another weak point to the study included the fact that statin therapy was likely stopped at one month after pregnancy was diagnosed not taking into account, late anomalies that could potentially occur.

Hastie et al. (2021) performed a registered-based cohort study using data obtained from the Swedish Pregnancy Register to investigate the association between aspirin use and bleeding during pregnancy and delivery. In 2013, only Stockholm and Gotland regions were included in the register, these areas represent less than one-third of deliveries. However, since 2014, the Swedish Pregnancy Register covers 16 to 20 regions in Sweden (covering 90% of all deliveries) and 98% of all deliveries within the 16 participating regions. Prospective data was collected from the Swedish Maternal Health Care Register; the Swedish National Quality Register for Prenatal Diagnosis; and neonatal records. Data was collected from the first prenatal visit to the scheduled follow-up 2 to 3 months postpartum.

Women included in the study gave birth between January 2013 – July 2017. If there was a woman who gave birth several times during the study period, only the last pregnancy and delivery were included. Women who were missing maternal prenatal health records and women

with records that reported the use of low-molecular-weight heparin or selective serotonin reuptake inhibitors were excluded from this trial, this left 313,624 women eligible for the study. Maternal demographic variables were extracted to include age at delivery categorized as less than 18, 18-34 years, and greater than 35 years, BMI was calculated from measured weight and self-reported height registered at the first prenatal visit, which then was divided into two groups, less than 30 or greater than 30 kg/m^2, and years of education was also obtained and self-reported by participants. The breakdown of education was categorized as less than 9 years, 10-12 years, and greater than 12. They defined occupation as either employed or government assistance (sick leave, student, or unemployed). Daily smoking was recorded at the first prenatal visit and the use of alcohol within 3 months before conception was recorded at that time as well. The data on aspirin use was obtained from prenatal care records, including the first prenatal visit record and from each subsequent prenatal care visit, which typically included 8-10 visits across the entire pregnancy. The definition of aspirin use during this study was self-reported use of aspirin at any visit during pregnancy.

Bleeding complications were recorded in prenatal or delivery records via the Swedish version of ICD-10, which categorized into bleeding complications during pregnancy, such as hematemesis, hematuria, bleeding from the airways, antepartum hemorrhage, and labor and postpartum complications, such as excessive intrapartum bleeding, postpartum hemorrhage (blood loss greater than 1000 mL recorded in birth records or by ICD-10 code 072), postpartum hematoma, and neonatal intracranial hemorrhage, these were keyed as the primary outcome. Additional analyses were done to better establish a measurement of bleeding risk by mode of birth, this was used to stratify the difference in bleeding risk between vaginal birth or cesarean delivery to examine labor and postpartum outcomes. Women with preeclampsia were excluded

from the analysis to better ensure that aspirin was being compared instead of other potential complications. The report investigated potential reporting bias by performing additional analyses of maternal complications unrelated to bleeding (pelvic girdle pain) and associations between paracetamol use and bleeding complications. These two factors have no known biological association with bleeding risk. Aspirin users and nonusers were compared via bivariate analysis using the Pearson chi-square test for categorical data and the Student t-test for continuous variables.

There were 313,624 patients included in the study and of these 4088 reported aspirin use during their pregnancy. It was concluded that women using aspirin were older, more obese, and more frequently parous than women who did not take aspirin. Aspirin therapy is often recommended to this population of women during pregnancy. In addition, aspirin users were more likely to have multiple pregnancies, to have conceived through IVF, and to have had a previous c-section. Women using aspirin had a higher rate of preexisting medical conditions (including hypertension and diabetes) and pregnancy complications, such as preeclampsia. Women who had used aspirin during their pregnancy had higher rates of preterm delivery and induction of labor and were more likely to have a cesarean delivery. The incidence of antepartum hemorrhage among women using aspirin was 2.4% compared with 1.8% among nonusers, which resulted in a crude odds ratio of 1.33 (95% CI, 1.09-1.63). After adjusting via IPTW, the association was no longer significant. In addition, aspirin use was not associated with gastritis the compound outcome of hematemesis, hematuria, or bleeding from the airways. The incidence of bleeding during labor was 2.9% among women using aspirin and 1.5% in non-users. Postpartum hemorrhage was also increased among aspirin users with 10.2% of aspirin users experiencing postpartum hemorrhage compared to 7.8 % of non-users. Women using aspirin

were more likely to develop a postpartum hematoma, aspirin users were 0.4% more likely compared to 0.1% in nonusers. After data was stratified for a mode of birth it was found that there was no association between bleeding during labor after vaginal or cesarean delivery. There was found to be an increase in postpartum hemorrhage among aspirin users who gave birth vaginally but not among users who gave birth via cesarean delivery. Women giving birth vaginally that were using aspirin were more likely to experience postpartum hematoma and have an infant with neonatal intracranial hemorrhage. Women who gave birth via cesarean delivery had no increase in postpartum hematoma or neonatal intracranial hemorrhage when taking aspirin. The study's overall findings showed an increase in bleeding complications in the postpartum period among women receiving aspirin therapy and giving birth vaginally. There may also be an increased risk of neonatal intracranial hemorrhage and maternal postpartum hematoma, but the numbers in this study were low.

This study was strengthened by the fact that it was a population-based study with data recorded from recent years. Given that the exposure to aspirin was based on self-reporting which could be considered a strength or a weakness, as there are no third-party dispensing drugs, which could lead to an increased likelihood that the participants are taking aspirin. The number of participants in the study was large which allowed for analyses of subgroups. The weaknesses of the study lie in the fact that it is not a randomized control study. To overcome potential biases arising from unbalanced maternal covariates, the individuals of the study used a propensity score and inverse probability weighting approach. This effectively improved the balance of the maternal covariates between aspirin users and nonusers and reduced the potential for bias.

Discussion

Aspirin therapy for the prevention of preeclampsia has long been recommended by medical associations such as the American College of Obstetricians and Gynecologists (ACOG) and the United States Preventive Services Task Force (USPSTF). This therapy method now has numerous studies outlining the efficacy in the prevention of preeclampsia and the decrease in preterm birth from this common pregnancy complication. Pravastatin, an HMG-CoA reductase inhibitor, also has some advantageous studies showing its potential usefulness in the prevention of preterm delivery in patients with risk factors for developing preeclampsia. While there are no current studies that compare these two medications side by side, the collection of data that has been reviewed gives insight into both the ability of the medications to prevent preterm delivery while also diving into the potential side effects associated with each treatment during pregnancy.

The question that must be discerned: Is there any comparison between aspirin and pravastatin when it comes to the ability to prevent preterm delivery? Aspirin has been the therapy of choice for many providers to help prevent patients with moderate/high-risk factors from developing preeclampsia and has subsequently been used to prevent preterm delivery, often a complication of preeclampsia. Aspirin therapy has been studied for many years and has been deemed a safe preventative treatment for pregnant women. The use of aspirin therapy has been shown to decrease the risk of preterm preeclampsia in women with high-risk factors commonly associated with the condition (Rolnik, et al 2017). Aspirin therapy initiated between 6 weeks through 13+6weeks gestation decreases the risk of preterm delivery (Hoffman, et al. 2020). These studies with data obtained in the last 5 years show the efficacy of aspirin therapy.

In comparison, pravastatin for the prevention of preeclampsia and preterm delivery has not been studied in as much detail as its aspirin counterpart but has shown some promise when it comes to the prevention of preeclampsia. This promise is especially seen in the double-blind

pilot study done by Costantine, et al. (2021), when 20 mg of pravastatin is administered within 17 weeks of gestation there was statistical significance in reducing preeclampsia with severe features, the study also showed no correlation or significance in adverse outcomes of mothers taking pravastatin during their pregnancy, this provides an opening for more studies to be completed in the future. A study performed by Ahmed et al. (2019) investigated the circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic protein made by the placenta, and found that using pravastatin during pregnancy could reduce the levels of sFlt-1. This is an important research factor as women with preeclampsia tend to have higher circulating levels of sFlt-1 which acts on the vascular endothelial growth factor and causes growth restriction in the fetus. The importance behind this blinded study was to prove or disapprove recent animal studies that showed promise with statins reducing sFlt-1 and thus decreasing the severity of preeclamptic symptoms. Unfortunately, this study showed no significance in the reduction of sFlt-1. Both medications have studies with data that is statistically significant proving the effectiveness of therapy in the prevention of preeclampsia, further studies are needed on pravastatin to truly see if drug therapy is effective in preventing preterm delivery.

Population studies on pregnant women tend to be limited due to ethical and societal expectations, it is often hard to justify putting them into clinical trials that could harm them or subsequently harm their unborn children. The question then becomes, how do we know that aspirin is safe to be used in pregnancy? Does the use of aspirin during pregnancy increase the mother's risk of adverse effects or the risk of adverse outcomes before, during, or after delivery for the fetus? Aspirin’s safety profile has been studied for many years and benefits have been shown to outweigh the risk in many women with an increased risk of preeclampsia. However, it is still shown to increase intrapartum bleeding during delivery, postpartum bleeding, and

postpartum hematomas in women who give birth vaginally (Hastie, et al 2021). There is also to data to support that aspirin use could be associated with an increased risk for neonatal intracranial hemorrhage (Hastie, et al 2021). The strength of aspirin observed in the study was 75-150mg, the data was not differentiated comparing the specific doses of aspirin and whether an increased dose increased the occurrence of bleeding during delivery, however, it would be assumed that an increase in the dose of aspirin would increase bleeding risk as well.

While studies suggest that aspirin therapy has benefits that outweigh the risk in its use for preeclampsia, such studies are not as readily available for pravastatin. HMG-CoA reductase inhibitors, or "statins" have long been considered teratogenic, not safe to use during pregnancy for harm to the fetus, and there has even been avoidance in using these medications for women of childbearing ages to help prevent any negative outcomes with unplanned pregnancies. Statin medication is generally used to lower cholesterol and that cholesterol is essential for fetal growth and development so therefore if the mother is taking medication to lower her cholesterol it could inherently affect the development of the fetus. Given the thought that these medications can harm the unborn child, it is hard to justify funding studies looking into their benefit or obtaining approval for study for that matter. However, studies of pravastatin, a hydrophilic type of statin, have suggested it is less likely to enter the embryo and has a smaller likelihood of adversely harming the developing fetus. A nationwide cohort study showed that statins may be used safely during pregnancy with no increased risk of congenital anomalies, but specific caution should be placed on watching for low birth weight and preterm delivery (Chang, et al 2021). The low birth weight and preterm delivery were less likely in the hydrophilic statins, such as pravastatin.

Further population-based studies have been done to investigate women that had used statins right before pregnancy, women who used statins during pregnancy, and women that

transitioned to a fibrate medication to control their increased cholesterol after finding out they were pregnant. There did not seem to be any correlation between the use of hydrophilic statin medication, such as pravastatin, during pregnancy and an increased risk of congenital birth defects (Ofori, et al 2007). Pravastatin was used in approximately twenty percent of the patients in this study with no additional increase in abnormal findings on maternal prenatal visits, or maternal outcomes. Given the history of adverse outcomes between aspirin and pravastatin, there becomes an increase in questions, which medication is safer? Is there a chance that they could both be useful in the prevention of preeclampsia? Is one truly better than the other?

Overall, there is research that suggests that pravastatin may have some benefit in the prevention of preeclampsia and preterm delivery, however, studies are limited. One randomized pilot-controlled study did show that preeclampsia and preterm births were not increased with pravastatin use and that it may have helped prevent preeclampsia and prolong gestation (Constantine, et al 2021). The evidence is compelling enough to suggest that research should be continued into the benefit that pravastatin can have in high-risk pregnancies, as the rates of cardiovascular disease rise, this will give women a chance to continue their current medication regimes without putting their future fetuses at risk if they decide to pursue pregnancy. Aspirin is still considered the tried-and-true method to reduce the rate of preeclampsia and help more mothers carry to term. The side effects of aspirin therapy have the potential to be overlooked when prescribing this common medication, especially when trying to prevent preeclampsia, which could have fatal consequences for the fetus and mother. No direct comparison studies have been done between pravastatin and aspirin to prevent preeclampsia and preterm delivery, making it difficult to fully compare them. Since aspirin has been more widely studied, it is more widely used and more accepted in high-risk populations, making it the favored drug of the two.

Until more studies are done to show the efficacy and safety of pravastatin, aspirin will likely stay the gold standard of treatment.

Conclusion

Prevention of preeclampsia has remained relatively stable and unchanged over the last two decades with low-dose aspirin therapy at the forefront of prevention. Not only has low-dose aspirin been used to help prevent preeclampsia in moderate to high-risk populations it has also been shown to reduce the risk of complications of preeclampsia such as preterm delivery. The adverse effects of aspirin therapy do show an increased risk of postpartum bleeding, but this is not significant enough to stop the use of this therapy.

Although, pravastatin therapy has not shown as much promise in its recent clinical trials it still provides a promising push in the right direction by providing potential new options for preeclampsia prevention. Recent studies have shown that it could be a safe way to manage dyslipidemia during pregnancy and that it may not be a teratogen as previously thought. There has yet to be a proven benefit of therapy in the prevention of preeclampsia or the prevention of preterm delivery but with time and more studies maybe this could be a new discovery. Constantine et al. (2021) suggest more research on the efficacy of pravastatin and with new improvements to medicine every day, there may be a change to the prevention of preeclampsia and its current protocol. However, overall, aspirin therapy is more suitable when it comes to preventing preterm delivery and providing some protection against developing preeclampsia in moderate to high-risk individuals.

Application to Clinical Practice

Aspirin therapy will continue to be prescribed to those patients at risk of developing preeclampsia as it has proven to be safe and effective. Women should continue to receive aspirin

therapy between 12 and 16 weeks and blood pressure should be monitored at every visit. Until more clinical trials can be done on pravastatin it will continue to be marked as teratogenic and unsafe to use during pregnancy.

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