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The safety and efficacy of pravastatin in the treatment of preeclampsia

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The Safety and Efficacy of Pravastatin in the Treatment of Preeclampsia

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Abstract:

Objective: Assess the efficacy of pravastatin in the prevention or treatment of preeclampsia in women who are at risk. **Design:** Systematic literature review. **Methods:** A search was performed using Pubmed utilizing the terms preeclampsia and pravastatin. The results were limited to studies that were double blind and placebo controlled and that occurred in the last 5 years. **Results:** None of the studies found statistical significance in the rate of preeclampsia between the experimental and control groups. Only one study found statistically significant differences in fetal birth weight and age at delivery. The other two studies found no differences between groups in severity of preeclampsia, gestational age, fetal birth weight and sFlt-1 levels. The studies found no harm was caused by the Pravastatin when given during pregnancy. **Conclusion:** These studies established preliminary safety and pharmacokinetics with the use of Pravastatin in pregnancy. The significance of the difference in the administration of Pravastatin in pregnancy could not be established in any of the studies. In order to establish any benefits of Pravastatin during pregnancy larger studies must be performed.

Introduction:

Preeclampsia is a multisystem complication of pregnancy characterized by high blood pressure and signs of end organ damage. Preeclampsia affects 3-5% of pregnancies and continues to be a cause of both maternal and fetal morbidity and mortality[1]. The pathophysiology of preeclampsia begins with placental release of soluble fms-like tyrosine kinase-1 (sFlt-1) and causes maternal angiogenic imbalance, inflammation, and endothelial dysfunction[2]. These changes result in new onset hypertension, proteinuria, and signs of end organ damage including retinopathy and swelling of the hands and feet[2]. Risk factors of preeclampsia include diabetes, high blood pressure, kidney disorders, autoimmune disorders, and multifetal gestation[3].

Preeclampsia is associated with serious and sometimes fatal outcomes for both mother and baby, and are dependent on the severity and timing of presentation. Mothers experiencing preeclampsia are at risk for permanent organ damage, seizures, and death[4]. Due to its placental origin, the fetus is at risk for hypoxia, preterm birth, and death[5]. The only definitive treatment is delivery of the fetus, therefore symptom and blood pressure management are essential throughout the pregnancy[6]. Methyldopa and Labetolol are considered safe anti-hypertensives during pregnancy, however, pharmacological approaches towards prevention have mixed results. Preeclampsia has similar origins to adult cardiovascular disease, and recent literature has proposed the use of CVD treatment such as statins in the prevention of preeclampsia.

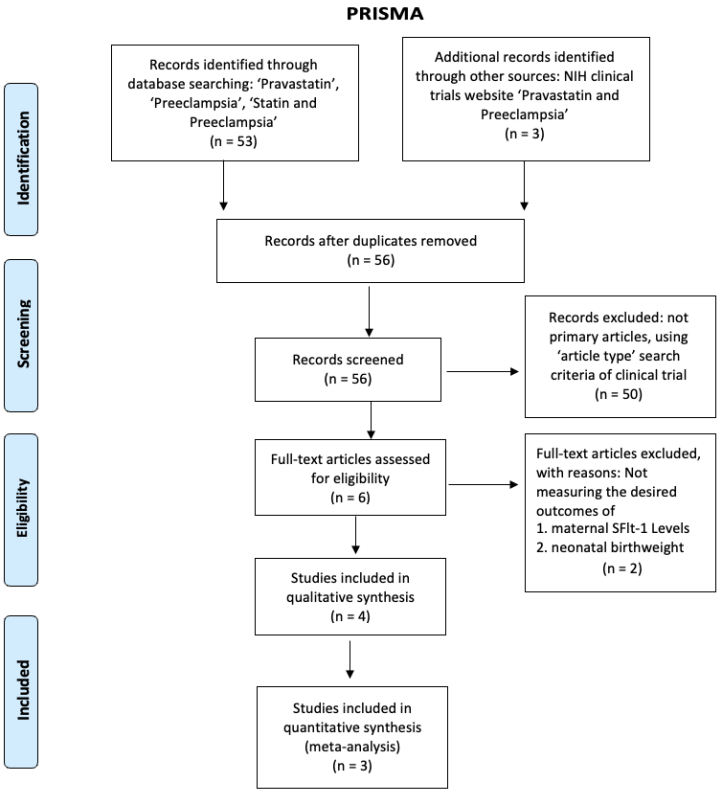
Statins are HMG-CoA reductase inhibitors used in both primary and secondary prevention to decrease serum lipid levels[7]. Statins also have pleiotropic cardioprotective effects including plaque stabilization, inflammation reduction and improved endothelial function[7]. Although there are many cardiogenic benefits to statins, HMG-CoA reductase inhibitors are classified as Category X in pregnancy. Cholesterol and it's substrates are essential for growth and development of the fetus, and reports of congenital abnormalities with statin use in pregnancy include anal atresia and transesophageal fistula[7]. Many of these studies examine statin use in the early gestational period, and recent literature exploring mid-late gestation period statin use has shown no such correlation. Karalis and colleagues performed a systematic review of teratogenic effects of statins during pregnancy indicating no correlation of congenital abnormalities with statin use[5]. To further investigate the benefits of statins in preeclampsia, researchers have used animal models to focus on the pleiotropic effects in the reduction of sFlt-1 levels. Recent literature has cited investigations of Pravastatin use in the prevention of

preeclampsia due to it's hydrosoluble structure limiting transport across the placenta. This makes the safety profile of Pravastatin superior in comparison to other statins[8].

This raises the clinical question, In pregnant women at high risk for preeclampsia, does pravastatin treatment improve sFlt-1 for preeclampsia and fetal birth weight compared to standard preeclampsia treatment? The following meta-analysis explores various clinical trials to answer this clinical question.

Methods:

An initial search of Pubmed was performed in September 2021 using the keywords "preeclampsia AND Pravastatin" which yielded 56 results. Limits included randomized control trials and recent within the last 5 years which then yielded 6 results. The inclusion criteria were human studies that were randomized and double blind with measured outcomes of SFlt-1 levels to determine the severity of the preeclampsia and fetal birth weight. After these constraints were applied 4 studies remained, but one had not been peer-reviewed at the time of the search so the final three remaining articles were chosen to be included in the meta-analysis. Quality assessment criteria included randomized placebo controlled studies of pravastatin, consideration of statistical power, and similar outcomes measurements of sFlt-1 levels, maternal and fetal outcomes. There was heterogeneity of studies due to statistical power differences. Statistical methods evaluated relative risk and hazard ratios.



Results:

Study 1: A Randomized pilot clinical trial of pravastatin vs. placebo in pregnant patients at high risk of preeclampsia. Constantine et al. [9]

The objective of this study was to evaluate the pregnancies of women who were at high risk for preeclampsia in a randomized control trial with Pravastatin vs placebo. The study looked at safety and pharmacokinetics of Pravastatin during pregnancy and it compared fetal and maternal outcomes in the experimental vs control groups.

This study included 20 women who were over 18, singleton with non-anomalous pregnancies. All the pregnancies at the beginning of the study were between 12+0 weeks and 16+6 weeks of gestation which was confirmed by ultrasound. The participants were all

considered high risk for preeclampsia because they had a previous pregnancy with documented severe preeclampsia that required delivery before 34 + 6 weeks. Exclusion criteria included: women with pregnancies with fetal genetic or major malformations, fetal demise, multifetal gestation, those with contraindications for statins, concomitant therapy with fibrates, niacin, cyclosporin, clarithromycin or erythromycin, HIV infection, history of solid organ transplant, chronic renal failure, uterine malformations, cancer or participation in another study. Before randomization all the participants had their AST and ALT drawn to ensure their livers were normally functioning. 10 participants were placed in the experimental group and were given 20mg of Pravastatin daily until delivery and 10 participants were placed in the placebo group and were given identical capsules. All patients continued their prenatal care under the supervision of their physician.

Statistical analyses were performed using the Wilcoxon rank-sum tests to analyze continuous variables with mother, fetal outcomes and the chi-square and Fisher exact test was used to analyze categorical data.

The results showed that the Pravastatin group had no congenital anomalies and the pharmacokinetics of Pravastin appeared to be safe during the second and third trimester. None of the mothers in the experimental group experienced rhabdomyolysis or liver injury. In the Pravastatin group 2 (20%) participants developed preeclampsia without severe features and 3 (30%) had a preterm delivery. In the control group 5 (50%) developed preeclampsia and all 5 had severe features. 6 (60%) had a preterm delivery. The statistical analysis between the group rates of preeclampsia had a relative risk of 0.22 with a confidence interval of 95% and a P of 0.03. The relative risk is < 1 which indicates the Pravastatin is protective and the P is < 0.05 which indicates the findings are significant. In the Pravastatin group the birthweight and age at

delivery were both statistically significant when compared to the control group. SFlt-1 levels were obtained as a quantitative measure of the reduction in preeclampsia precipitated by the statins. This measurement was one of the criteria used to help determine if a participant was experiencing preeclampsia. Overall the SFlt-1 levels were lower in the mothers who took the Pravastatin, but statistical analyses on this measurement alone were not performed to determine if it was a significant difference.

This study showed promise with the safety and efficacy of using Pravastatin to prevent preeclampsia. It lacks statistical power because the study groups are too small to accurately represent the overall population of pregnant women with preeclampsia. The significant results in this study cannot be applied across all populations, but the results can be applied to future studies with larger sample sizes.

Study 2: Pravastatin versus placebo in pregnancies at high risk of term preeclampsia. Döbert et al. [10]

The objective of this study was to investigate if pravastatin given between 35 to 37 weeks gestation until delivery would reduce the rates of preeclampsia in women who are at high risk in late term pregnancy. The primary outcome was whether or not the women had preeclampsia at the time of delivery. Secondary outcomes included neonatal birth weight, gestational age and material SFlt-1 concentrations. The side effects experienced by the women in the experimental group were also closely monitored.

This study was a multicenter, double blind randomized placebo controlled study with 1120 participants. The placebo group had 543 of these participants and the experimental group had 548 participants. All of the participants were over 18 with singleton pregnancies and were considered high risk for preeclampsia based on demographics, medical history, mean arterial

pressure, maternal serum placental growth factor and SFlt-1 levels. Participants that were severely ill, had major fetal abnormalities, had a planned delivery within 7 days or had established preeclampsia were excluded.

Statistical analyses for this study included a Kaplan-Meier curve to estimate the incidence of preeclampsia. A mixed effects Cox regression was also performed which adjusted for the fixed effect of the risk of preeclampsia at screening and random effects for participants. P values were obtained from a likelihood ratio test for interactions with treatment. Binary outcomes were analyzed with log-binomial regression analysis. SFlt-1 concentrations were analyzed with ANCOVA or the log-transformed concentrations with adjustments for baseline levels.

The cox-regression for the primary outcome of pravastatin lowering the incidence of preeclampsia showed no significance (P= 0.65). The statistical analysis of the secondary outcomes of neonatal birth weight, gestational age and material SFlt-1 concentrations also showed no statistical significance between the groups. There was 1 serious adverse event in the Pravastatin group and 1 serious event in the placebo group.

This study had a larger sample size which was more representative of the larger population. This gave it more power, but statistical analysis found that the confidence interval for the primary outcome was 0.78, so the power of the study was lower than expected. The study is also limited because of when Pravastatin was given to the participants. Due to this the results may be limited because of the limited time the participants could take the Pravastatin. This study found no harm caused by the Pravastatin so it still leaves the door open for future studies. This study should not be used to rule out benefits from Pravastatin for women at risk of preeclampsia because it was only looking at late pregnancy.

Study 3: Pravastatin for early-onset preeclampsia: a randomized, blinded, placebo-controlled trial. Ahmed et al. [11]

The objective of this study was to examine the effect of pravastatin on plasma sFlt-1 levels in pregnant women with preeclampsia via a randomized, blinded placebo-controlled trial. Outcomes included maternal safety measured by serum sFlt-1 levels, sFlt-1:PIGF ratio. Time from randomisation to childbirth was also used as a measured outcome. During pregnancy, fetal safety was measured by cardiotocography, umbilical cord blood flow, and amniotic fluid volume. Fetal safety during childbirth include APGAR score, birthweight, and incidence of premature neonatal complications including fetal death.

This study included 62 participants with early-onset preeclampsia categorized as ages 24+0 and 31+6 weeks gestation. Other criteria for inclusion were a minimum of 18 years of age, a single viable fetus with no major anomalies. Preeclampsia was defined as new onset hypertension and new onset proteinuria of 2+ on a standard dipstick and further confirmed with a spot protein:Cr ratio >30mg/mmol. Exclusion criteria were women already taking statins, if there was a contraindication to statins, or if fetal survival was not likely 48 hours post-diagnosis. Participants were randomly assigned to daily pravastatin (40mg) or placebo in a 1:1 ratio via computerized minimized randomization procedure to achieve balance between groups for gestational age, smoking status, and severity of hypertension.

Statistical analysis was performed with intention-to-treat. Kaplan Meier curves were constructed for time from randomisation to childbirth, and a Cox proportional hazards model was used to determine hazard ratios. Variables considered in a multivariable Cox proportional hazard model included gestational age at diagnosis, systolic and diastolic blood pressure, PIGF, sFlt-1, proteinuria, uric acid, and platelets.

Although not statistically significant, results reveal maternal plasma sFlt-1 levels were lower in the pravastatin group when compared to placebo (292 pg/ml, 95% CI 1175 to 592; P = 0.5). No differences were found between groups when examining PIGF levels, or sFlt-1:PIGF ratio. Pravastatin prolonged the gestational age in comparison to placebo (hazard ratio [HR] 0.84; 95% CI 0.50–1.40) but this difference was not significant (P = 0.6). Maternal blood pressure and other biochemical parameters did not differ between groups over the first 3 days and up to day 14. Markers of fetal growth including umbilical artery pulsatility index did not differ between groups. There were three perinatal deaths in the placebo group, and none in the pravastatin group.

This study revealed prolonged pregnancy by 4 days in women taking pravastatin, which is a significant number for premature fetuses <32 weeks of age. Although not statistically significant, this study is the beginning of many to examine the efficacy and safety of pravastatin in reducing negative outcomes in preeclampsia.

Table 1. Overview of studies included in the meta-analysis.

Study	Study Type	Number of participants	Time of Admin	Maternal outcome	Fetal outcome
Constantine et al. 2021	Blinded, randomized, placebo controlled	20	12+0 - 16 + 6 weeks	-Maternal adverse events from medication side effects -Pravastatin pharmacokinetic parameters -Rate and severity of preeclampsia -Maternal lipid profile -Maternal sFlt-1 -Placental growth factor (P1GF)	-Gestational age at delivery -Rate of preterm delivery -Birthweight -Auditory brainstem response
Dobert et al. 2021	Double blind, placebo,	1120	35-37 weeks	-Delivery with preeclampsia -Adverse pregnancy	-Stillbirth or neonatal death

	randomized			outcomes -Maternal serum sFlt-1 levels -Creatinine Kinase	-Neonatal morbidity -Birthweight
Ahmed et al. 2019	Blinded, randomized, placebo controlled	62	24- 31+6 weeks	-Plasma sFlt-1 levels -sFlt-1:P1GF ratio -Time from randomization until child birth -Preeclampsia (blood pressure, proteinuria, serum levels of creatinine, uric acid, albumin, liver transaminases, electrolytes, platelets, and those of maternal status were prothrombin time, C-reactive protein, haemoglobin and bilirubin)	-Birthweight -APGAR score -Gestational Age -Neonatal complications

Discussion:

Pravastatin is frequently used for its pleiotropic effects[7], however, this meta-analysis reveals no significant differences regarding its use to prevent preeclampsia. Using sFlt-1 as a biomarker, all studies were conducted as either blinded or double-blinded, and found no significant difference in maternal sFlt-1 concentration between women who took pravastatin or placebo. Constantine et al had the most promising results with the lowest statistical power, therefore cannot be applied across all populations. Dobert et al corrected this issue with a higher sample size but differed in regards to time of pravastatin administration, ultimately altering results. Ahmed et al found similar results despite poor medication compliance, a potential downfall to their reliability. All three studies showed minor improvement in sFlt-1 levels, although Constantine et al did not perform statistical analysis on this particular outcome (Dobert (1.08, 95% CI 0.78-1.49 P=0.65) and Ahmed (292 pg/ml, 95% CI 1175 to 592; P=0.05)).

All investigators chose similar secondary maternal and fetal outcomes including birthweight and neonatal complications. All three studies established preliminary safety and pharmacokinetics of the use of pravastatin in second and third trimester pregnancies due to lack of congenital abnormalities and serum pravastatin concentration levels. The Constantine et al pilot study focused on pharmacokinetics of pravastatin during pregnancy, showing consistencies in comparison to normal properties of pravastatin. All studies address the risk of congenital abnormalities with pravastatin administration during pregnancy to be congruent with placebo. Ahmed et al also discovered a 4 day increase in gestational age, although chance cannot be excluded. A limitation to the Dobert et al study was the timing of administration as seen in Table 1, administering pravastatin at 35-37 weeks gestation. Constantine et al started administration at 12+ weeks, and Ahmed at 24+ weeks. This discrepancy could explain the variations in results, and could have tremendous implications on pravastatins effectiveness as well as safety profile regarding fetal development.

Conclusion:

Administration of pravastatin to pregnant women with a single viable fetus and confirmed preeclampsia did not improve maternal sFlt-1 levels, and revealed a benign safety profile among all studies. Pravastatin may have a role in preventing preeclampsia in high risk populations but lacks evidence to be considered a first-line treatment. Future studies should investigate laboratory significance and further support safety profile before becoming a treatment of choice. Based on current data, the few benefits of pravastatin equate to the innocuous effects on the fetus, indicating the necessity of further research.

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