Original Article

Effect of Pravastatin use as a Prophylaxis for High Risk Preeclampsia Women on Pregnancy Outcome: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Preventing preeclampsia is crucial to lowering maternity mortality and morbidity rates globally. The use of to enhance maternal, perinatal, or newborn outcomes and avoid preeclampsia has been investigated in most recent studies. The outcomes remain up for debate, though.

Goals: To assess how well pravastatin works to keep pregnant women from developing preeclampsia.

Methods: To determine the likelihood of preeclampsia, this research included an analysis of randomized controlled trials (RCTs) of trials incorporating pregnant women given pravastatin versus placebo. PubMed, Science Direct, EMBASE, PROQUEST, and SCOPUS were searched for relevant literature. Five investigations were first found to match the inclusion criteria; however, two of them had to be disqualified since they were treatment studies, and one minor research only utilized pravastatin for just a few weeks, keeping just 2 articles for statistical analysis.

Results: Pravastatin prescription was linked to a lower incidence of preterm delivery (OR: 0.31; 95% CI: 0.16-0.58; p<0.01) and preeclampsia (OR: 0.51; 95% CI: 0.29-0.90; *p*=0.02). There was no difference in the risk of PE & fetal growth restriction and severe characteristics. Preventive pravastatin was linked to a notable and significant decrease in premature preeclampsia rates (OR: 0.034; 95% CI: 0.202-0.905), according to the only trial (INOVASIA) that examined premature preeclampsia. Pravastatin-treated pregnant women experienced improved perinatal outcomes, including reduced birth weight, Apgar scores, NICU admission, and respiratory distress syndrome.

Conclusions: Pravastatin may help pregnant women avoid preeclampsia, early delivery, and perinatal illness.

Key Words: High risk; pravastatin; preeclampsia; pregnancy; prophylaxis.

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INTRODUCTION

One of the primary causes of mother and neonatal death globally, preeclampsia affects 2–8% of pregnant women. With high maternal and birth-related deaths annually, preeclampsia is the main cause of infant and maternal mortality worldwide. Fetal growth restriction, stillbirth, and issues related to iatrogenic prematurity are the main reasons of preeclampsia's high rate of fetal-neonatal mortality[1,2].

The best way to lower maternal and neonatal mortality and morbidity is to prevent preeclampsia. The main medication for avoiding preeclampsia is aspirin[3,4]. Nevertheless, a number of recent meta-analyses and systematic reviews point to certain restrictions on aspirin's ability to prevent preeclampsia[5]. Despite nearly halving the incidence of early-onset preeclampsia, low-dose aspirin does not "eradicate" the condition and has no effect on term preeclampsia[6].

Furthermore, low-dose aspirin must be initiated prior to 16 weeks[7]. Researchers have started looking into other compounds to increase aspirin's effectiveness in avoiding preeclampsia[8–12].

Hypercholesterolemia is treated with a class of drugs that reduce cholesterol called statins. In the past, statins were categorized by the Food and Drug Administration (FDA) as category X, meaning that they should not be taken while pregnant[13]. To yet, however, neither human nor animal studies have shown that exposure to statins during pregnancy increases the incidence of congenital malformations or impairments[14].

Animal studies showing that pravastatin has a safeguarding impact on the uteroplacental barrier and vascular cells[15] support the use of statins for avoiding preeclampsia. Pravastatin's pleiotropic properties, which include immune-modulatory and anti-inflammatory qualities, as well as a decrease in the formation of free oxygen radicals and smooth muscle cell growth, may be helpful in minimizing preeclampsia[16].

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The FDA asked to have its warning list regarding taking statins & pregnant removed 3 years ago. Because of how safe it is during pregnancy, pravastatin has been studied more thoroughly than the other statin groups[13].

Pravastatin is probably the least detrimental to fetal development when compared to other statins because of its hydrophilic activity, low tissue penetration, and absence of hazardous reproductive consequences in animal trials. An early small series including pregnant women exposed to pravastatin during the first trimester did not reveal any congenital abnormalities[17,18].

Pravastatin administered during pregnancy may help reduce dysfunction of endothelial cells, hypertension, renal damage, and cardiovascular problems in both the mother and the child following preeclampsia in a model involving mice. By boosting free circulating placental growth factors and decreasing the production of anti-angiogenic molecules, which are stimulated by cytokines, pravastatin could safeguard endothelial cells[18].

The maternal endothelial cells' dysfunction may be finally fixed by addressing the angiogenic imbalance. A lady with antiphospholipid syndrome (APS) was the subject of the first human trial suggesting that pravastatin might be helpful in preventing preeclampsia[19]. Preeclampsia may be prevented by pravastatin, according to these early data.

This study's main goal is to find out if giving pregnant women pravastatin can reduce their risk of preeclampsia more effectively than giving them a placebo or no intervention at all.

METHODS

Pravastatin's preventive utility in preventing preeclampsia was assessed by a review and meta-analysis of randomized clinical trials. A review question: Does taking pravastatin lower the chance of developing preeclampsia in high risk PE women?

Eligibility criteria

The inclusion criteria

1. randomized clinical trials;
2. pregnant women of any gestational age receiving pravastatin and a 2nd group receiving placebo;
3. studies conducted in between 2000-2024;
4. articles providing the risk or occurrence of preeclampsia between the intervention group and placebo group as an outcome.

The exclusion criteria

1. Inaccessible full-text;
2. non-English publications;
3. studies in women with established preeclampsia or gestational hypertension or fetal growth restriction;
4. Study forms other than RCTs (cohort, case reports, …etc.);
5. duplicated studies.

Sources of information and search methodology

Using MESH terms and phrases associated with pravastatin and PE (based on the PICO techniques), an electronic search was carried out from 2000 to 2024 across online databases such as Pubmed, Science Direct, EMBASE, PROQUEST, and SCOPUS.

Procedure for selection

Every database was screened according to the inclusion and exclusion criteria. To prevent selection bias, two reviewers independently searched the literature. A third investigator was included in the consensus that resolved any disputes.

Procedure for gathering data

Using a preset checklist that included the study design, baseline characteristics, interventions, and outcomes, two co-authors meticulously gathered data from each study. The third investigator then verified the findings.

Outcomes of the study

The primary outcome of this study: the chance of preeclampsia developing in the pravastatin and placebo groups. Preeclampsia is described as hypertension with one or more of the following new-onset circumstances at >20 weeks plus proteinuria, other maternal end-organ disorder, and utero-placental dysfunction. This diagnosis was made in accordance with the American College of Obstetricians and Gynecologists' (ACOG) guidelines[20].

The secondary outcomes of the study: premature delivery, babies that are tiny for gestational ages, severe characteristics of preeclampsia, and premature preeclampsia. Severe hypertension (>160/110 mm Hg), thrombocytopenia, poor liver function, renal insufficiency, pulmonary edema, headache that started suddenly, or vision disturbance were all considered signs of preeclampsia with severe characteristics. The development of preeclampsia

that leads to delivery before 37 weeks gestation was referred to as preterm preeclampsia. A delivery that occurred before 37 weeks of pregnancy was considered preterm. Birth weight less than the 10th population centile was considered small for gestational ages (SGA)[20].

Study risk of bias assessment

The Joanna Briggs Institute of University of Adelaide provided a clinical trial inventory with 13 questions to assess the research' quality (Figure 2). If the conditions were fulfilled, each item on the JBI checklist was given a score of one; if not, it was given a score of zero. For each of the selected studies, summary scores were calculated by adding the item-specific values. The quality of the investigations was then evaluated as good (≥8), fair[6-7], or bad (≤5) based on the summary scores. The risk of bias was evaluated separately by two individuals using JBI. Every team member was consulted about any issues until a compromise was achieved.

Statistical analysis

The Review Manager (RevMan) 5.4.1 program (Cochrane Collaboration, UK) was used to conduct statistical analyses. To calculate the Odd Ratio (OR) and 95% CI, a pairwise meta-analysis of preeclampsia risk was conducted between the pravastatin and control groups. A chi-square test (Cochran's Q statistic) was used to evaluate study heterogeneity, and Higgins' I2 statistics were used to quantify it. I2 values were utilized to determine the degree of heterogeneity, while a p-value of less than 0.1 from the chi-square test indicated statistical heterogeneity. I2 < 25% was considered low heterogeneity, 25–75% was considered moderate heterogeneity, while I2 > 75% was considered strong heterogeneity. If the I2 value was greater than 50%, the meta-analysis used a model with random effects. In the remaining circumstances, a model with fixed effects was employed. Because there were insufficiently few papers (n < 10), we did not conduct a publication bias assessment. Unless otherwise noted, all analyses were considered statistically significant if the *P-value* was less than 0.05.

RESULTS

Study selection

Following the initial screening of each database, as shown in (Figure 1), we found 1,202 articles, of which 72 were eliminated due to repetition. Ultimately, four pieces satisfied the requirements for inclusion. INOVASIA and the US OPRC Study[21,22], two of the four studies that were part of the systematic review, are the only two that can be examined using meta-analysis since they were the only ones that examined the main consequences of preeclampsia and gave pravastatin from the beginning of pregnancy until delivery.

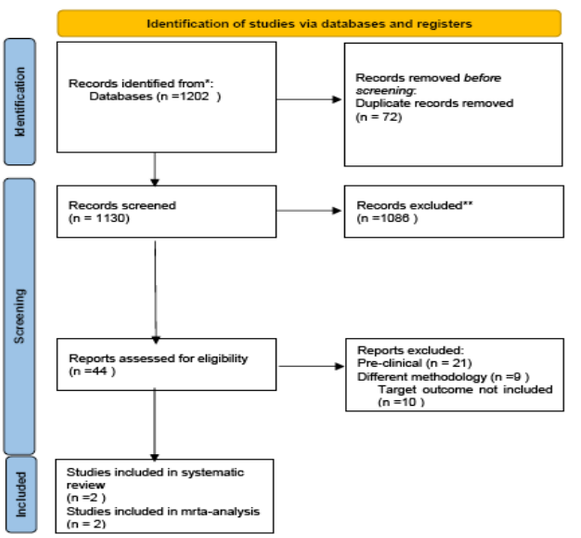

Fig. 1: PRISMA flowchart of included researches

Features of the study

(Table 1) provides a summary of the features of the included studies. Eighty-five of the 1,734 individuals in the four RCTs were given pravastatin, while the remaining 849 were control subjects.

Table 1: displays the attributes of these four investigations

References	Study Design	Intervention	NO.	Result
Studies analyzed in the Meta-analysis				
(Costantine *et al* 2021)[21] (US OPRC Study)	RCT	women high risk of PE (gestational age from 12 to 16+6 weeks) given pravastatin 20 mg/day vs. placebo orally till birth.	40	PE prevalence in pravastatin vs. placebo group (10% vs. 45%). Occurrence of severe PE in pravastatin vs. placebo group (0 vs. 40%).
Akbar *et al*, 2022b[22] (INOVASIA)	RCT	Controls (received low-dose aspirin (81 mg)/ day & calcium (1 g/day), vs. intervention (received pravastatin 20 mg two times per day in addition) from 14 wks. until delivery or preeclampsia.	173	Pravastatin arm had a significantly lower rate of premature PE (13.8% vs. 26.7%, p=0.034) & premature delivery (16.1 % vs. 36, p=0.003) %
Study incorporated only in systematic review				
Hassanain *et al*.,2018[23]	RCT	Pravastatin 10 mg once daily vs. placebo for a month duration starting from the 13th week	400	PE (6 vs. 16 women) and severe PE (4 vs. 11 women) rates in pravastatin arm were lower contrasted to placebo.
Dobert *et al*., 2021[24]	RCT	Singleton pregnancies with high risk of PE , pravastatin 20 mg, daily vs. placebo, from 35 up to 41 weeks or delivery	1121	PE occurred in 14.6% of pravastatin and 13.6% in the placebo arm. Pravastatin did not affect incidence of other placental mediated diseases (e.g: Gestational hypertension, stillbirth, abruption, FGR) or neonatal morbidity& mortality

Bias risk in research

According to the JBI evaluation, three completed studies had good quality, and the final one had fair quality. Since none of the studies received a summary score of five or lower, none were classified as low quality. (Figure 2) displays the JBI assessment's findings.

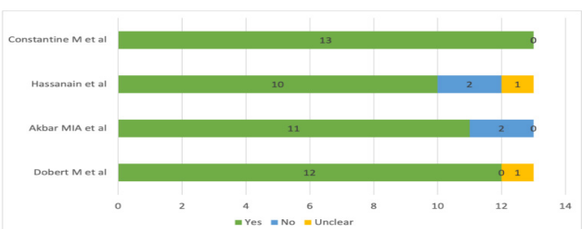

Fig. 2: The Joanna Briggs Institute Checklist for Study Quality

Results of studies as individually analyzed

Preeclampsia (PE)

Hassanain *et al*. (2018) show that pravastatin-administered groups had a lower incidence of preeclampsia (3% vs.8%; *p*=0.028); however, pravastatin was only used for short periods of time (4 weeks) in this study[23]. Pravastatin does not appear to lower the incidence of term preeclampsia (14.6 vs. 13.6%; *p*=0.65), according to Dobertz *et al*. (2021); however, this trial was eliminated because the patients were already hypertensive before taking pravastatin.

Preterm preeclampsia

The outcome was only assessed by INOVASIA[22]. Pravastatin treatment dramatically decreased the rate of premature preeclampsia (<37 weeks) in the INOVASIA trial (13.8% vs. 26.7%; p=0.034; OR=0.034, 95% CI: 0.202-0.905).

Neonatal outcomes: Pravastatin was associated with superior perinatal–neonatal outcomes in comparison to the untreated group, including higher birthweight, improved Apgar scores, decreased NICU admission, decreased NICU duration of the stay, and respiratory distress syndrome according to Akbar *et al*., 2022b & Costantine *et al*., 2021.

In meta-analysis

Pravastatin treatment was linked to a lower risk of preeclampsia in general (OR: 0.51; 95% CI: 0.29-0.90; *p*=0.02) (Figure 3).Yet, pravastatin-administered groups did not have a lower risk of severe preeclampsia (*p*=0.06) (Figure 4). A significantly lower incidence of premature delivery was linked to pravastatin (OR: 0.31; 95% CI: 0.16-0.58; *p*<0.01) (Figure 5). The risk decline of small for gestational ages was not linked to pravastatin (*p*=0.26) (Figure 6). Research on the results of preeclampsia and preeclampsia with severe characteristics showed a substantial degree of variability (I2 > 50%). The results of premature preeclampsia, premature delivery, and intrauterine growth retardation did not differ from one another.

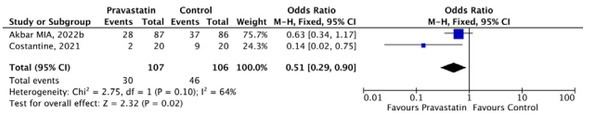

Fig. 3: Pravastatin's impact on preeclampsia risk in a forest plot

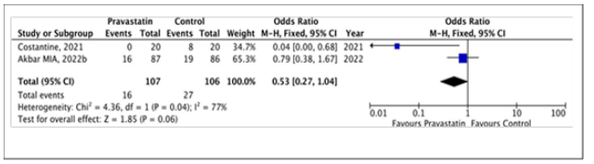

Fig. 4: Pravastatin's impact on the possibility of severe preeclampsia forest plot

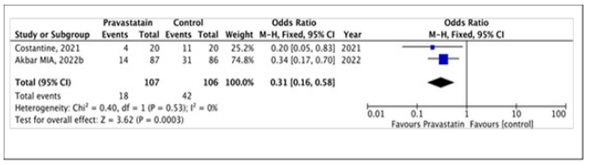

Fig. 5: Pravastatin's impact on the likelihood of premature delivery is seen in a forest plot

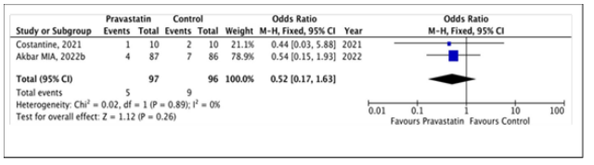

Fig. 6: Pravastatin's impact on the likelihood of fetal growth restriction is shown as a forest plot

DISCUSSION

Pravastatin's advantages in lowering the likelihood of preeclampsia in expectant mothers have been demonstrated by this systematic review and meta-analysis. Based on the findings of this meta-analysis, pregnant women who take pravastatin as a preventative measure have a significantly lower risk of developing preeclampsia. This claim was supported by the two most pertinent RCTs, the US OPRC study (n = 40) and the INOVASIA study (n = 173). Pravastatin was administered to high risk PE pregnant women in both trials for a sufficient amount of time (from the late first trimester till birth).

According to the US OPRCS (10% vs. 20%) and INOVASIA (32.3% vs. 43%) trials, preeclampsia is less common in pravastatin cohorts. The treatment strategies used in these trials varied somewhat. INOVASIA used a larger dosage of pravastatin (40 mg/day) than the US OPRC trial (20 mg/day). In contrast to the INOVASIA research (14–20 weeks gestation), pravastatin was given sooner in the US OPRC study (12+0 till 16+6 weeks). The US OPRC's goal was to assess the pharmacokinetics and safety of pravastatin, while INOVASIA's main goal was to assess the drug's ability of avoiding preeclampsia.

Considering the other two trials used a different intervention strategy, they were not included in the subsequent meta-analysis. In these investigations, pravastatin was administered either too soon or too late. Pravastatin was given to women who were already hypertensive in weeks 35–37–41 of the Dobert study[24], which was too late in the pregnancy. It should be mentioned that the UK STAMP study, the initial therapy study, also had unsatisfactory results. Pravastatin was only given throughout the very brief treatment duration of 13–16 weeks of gestation in the Hassanain research[21].

Compared to the other two RCTs, when pravastatin was provided from the late 1st trimester and early 2nd trimester till birth or preeclampsia developed, this trial's duration was too short. Pravastatin was shown to dramatically reduce the probability of premature preeclampsia in the INOVASIA study[22]. For both the mother and the babies, premature preeclampsia, especially early-onset preeclampsia, has more serious short- and long-term effects. An increased risk of fetal growth restriction, perinatal mortality and morbidity, placental pathology, anomalous uterine artery and umbilical artery Doppler, and death of the mother is linked to premature or early-onset preeclampsia[22].

Furthermore, compared to term preeclampsia, early-onset preeclampsia increases the mother's chance of developing subsequent illnesses, especially cardiovascular disease[25]. Pravastatin's capacity to lower the likelihood of early onset preeclampsia will considerably lower the risk of infant and mother death and morbidity brought on by this condition.

Pravastatin did not lower the likelihood of preeclampsia with severe symptoms, according to this meta-analysis (p=0.06). According to the US OPRC experiment, the pravastatin group had a significantly lower prevalence of preeclampsia with severe symptoms (0 vs. 40%; p=0.003). The proportion of preeclampsia with severe symptoms, nevertheless, did not change, according to the INOVASIA trial (18.4 vs. 22.1%; p=0.305).

Furthermore, our meta-analysis shows that the pravastatin group had a significantly lower rate of premature birth. The only studies that reported on premature delivery outcomes were the US OPRC study and the INOVASIA trial. Both the US OPRC study (20% vs. 55%; p=0.04) and the INOVASIA trial (16.1% vs. 36%; p=0.01) had considerably decreased rates of preterm births. The lower rate of severe preeclampsia in the US OPRC and INOVASIA trials, which would otherwise require an early iatrogenic delivery, may help to explain these results[21,22]. Because severe preeclampsia morbidity (HELLP syndrome, eclampsia ,…etc.) was common, the high rate of premature birth in preeclampsia cases was primarily an iatrogenic justification. The risk of premature birth will go down if severe preeclampsia is less common.

Another reason is because in INOVASIA investigations, the pravastatin group experienced a decreased incidence of premature preeclampsia. Pravastatin may also postpone the development of preeclampsia by a mean of 10 days, according to the INOVASIA research[22].

The two trials indicate a tendency for the pravastatin group to have better newborn outcomes than the control or placebo group, despite the fact that they were not statistically examined. The pravastatin group saw significantly decreased rates of neonatal morbidity, including duration NICU hospitalization, ventilator aid, respiratory distress syndrome, intraventricular bleeding, and infection. Furthermore, there was no variation in the two groups' rates of congenital anomalies in all trials. Pravastatin's risk profile throughout pregnancy is supported by these findings[21,22].

Pravastatin's pleiotropic influence on the pathophysiology of preeclampsia is probably what causes its beneficial effects on pregnancy outcomes[26,27].

By increasing growth factors production, and decreasing sFlt-1 and sEng levels, statins improve vascular Nitric Oxide synthesis[28]. A shorter pregnancy time frame, more severe types of preeclampsia, and unfavorable pregnancy outcomes are all significantly correlated with elevated levels of sFlt & plGF[29]. Pravastatin significantly improved preeclampsia biological markers, according to two publications relying on the INOVASIA trial[22,29]. During gestation, serum sFlt-1 levels rose significantly and PlGF levels diminished significantly in the placebo arm, whereas with pravastatin, these changes were negligible[22]. These results agreed with the US OPRC trial[21].

Mendoza *et al*.'s (2021) trial, which was excluded from the meta-analysis, also showed that women with early-onset fetal growth restriction who took pravastatin had a lower sFlt1/PlGF ratio than those who did not[30]. Because they raise the synthesis of Th2 anti-inflammatory cytokines while lowering that of Th1 pro-inflammatory cytokines, statins have also been demonstrated to have anti-inflammatory properties[16]. Serum IL-6 (pro-inflammatory) levels were shown to be considerably lower in the pravastatin group but remained unchanged in the control group in the Akbar *et al*. experiment[22].

Our study only included RCTs, which lessened the meta-analysis's bias. Yet, only 2 articles with a comparatively small number of participants were found for our study to be incorporated in the meta-analysis. Only the INOVASIA and US OPRC studies use appropriate methods (timing, length of time, dose, patient choice, and research methodology) to investigate the effectiveness of pravastatin in avoiding preeclampsia. There were additional restrictions on these two experiments. INOVASIA's control group wasn't given a placebo because of study budget limitations[22].

Even so, the INOVASIA researchers took a few extra precautions to reduce the possibility of bias. Since the main goal of the US OPRC trial was to evaluate the safety and pharmacokinetics of pravastatin, the occurrence of preeclampsia was not the main focus[21].

Pravastatin may lower the incidence of premature preeclampsia, early birth, and preeclampsia, according to this meta-analysis. Pravastatin additionally enhanced perinatal outcomes, most likely due to a lower rate of preeclampsia and premature birth. However, more studies with a sizable sample size and appropriate methods (double-blind, placebo-controlled, multicenter RCT) are needed to validate these findings. The best time, dose, and time frame for pravastatin treatment are among the several unknowns surrounding its use to avoid preeclampsia. Additionally, babies and neonates born to moms taking pravastatin need to be monitored both in the short and long term.

CONCLUSION

taking pravastatin was linked to a markedly lower incidence of premature delivery and preeclampsia. Pregnant women who take pravastatin have considerably superior outcomes for respiratory distress syndrome, NICU admission, NICU length of stay, birthweight, and Apgar scores. Premature preeclampsia, premature delivery, perinatal morbidity, and preeclampsia may all be prevented with the use of pravastatin.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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