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ARTICLE

EFFICACY AND SAFETY OF PRAVASTATIN IN PLACENTAL-RELATED DISORDERS: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Placental-related disorders impact over 33% of pregnancies. Several of these syndromes lead to higher rates of maternal and fetal death and morbidity and can have long-term health consequences. Several RCTs have found that pravastatin is associated with a significant reduction in the incidence of preterm preeclampsia and preterm birth. However, alternatives require substantial evidence. On the methods, two writers assessed the risk of bias. The Cochran test was used to assess heterogeneity among studies. The Mantel-Haenszel technique was used to obtain the results. The study's results were described using forest plots. The study used six randomized controlled trials. Findings showed a reduced risk of preeclampsia, preterm birth, and NICU admission in pregnant women taking pravastatin. There was no significant reduction in the risk of neonatal respiratory distress, congenital disorders, and adverse events of headache, heartburn, and musculoskeletal pain. This study suggests that pravastatin use may have beneficial effects in reducing the risk of placental-related disorders in patients.

Keywords: Placental-related disorders; Pravastatin; Prevention;

АБСТРАКТ

Плацентарные расстройства влияют на более чем 33% беременностей. Некоторые из этих синдромов приводят к более высоким показателям материнской и фетальной смертности и заболеваемости и могут иметь долгосрочные последствия для здоровья. Несколько РКИ показали, что правастатин связан со значительным снижением частоты преждевременной преэклампсии и преждевременных родов. Однако альтернативы требуют существенных доказательств. Что касается методов, два автора оценили риск смещения. Тест Кохрана использовался для оценки неоднородности среди исследований. Метод Мантеля-Хензеля использовался для получения результатов. Результаты исследования были описаны с помощью лесных диаграмм. В исследовании использовались шесть рандомизированных контролируемых испытаний. Результаты показали снижение риска преэклампсии, преждевременных родов и поступления в отделение интенсивной терапии новорожденных у беременных женщин, принимающих правастатин. Не было никакого значительного снижения риска респираторного дистресса у новорожденных, врожденных нарушений и нежелательных явлений в виде головной боли, изжоги и мышечно-скелетной боли. Наш вывод: это исследование предполагает, что использование правастатина может иметь благоприятные эффекты в снижении риска плацентарных расстройств у пациентов.

Ключевые слова: Плацентарные расстройства; Правастатин; Профилактика;

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INTRODUCTION

The placenta is a specialized organ that develops solely during pregnancy. The placenta facilitates the transfer of nutrients, gasses, and metabolic substances between the mother and the fetus. Placental-related disorders impact over 33% of pregnancies. Several of these syndromes lead to higher rates of maternal and fetal death and morbidity and can have long-term health consequences.[1,2] Placental-related disorders are characterized by specific symptoms that suggest the presence of disease and consequences.[3-5] Placental malfunction and programming can result in long-term health repercussions for both the mother and her children. In recent decades, the occurrence of placental-related disorders and diseases has seemingly risen due to factors such as delayed reproductive planning, higher rates of cesarean sections, and lifestyle changes, including an unhealthy diet. [6,7]

Statins have been widely utilized for reducing individuals' cholesterol levels for a considerable period of time. Pravastatin belongs to the first generation of statins. This compound has a high hydrophilicity, liver selectivity, and low potency as an HMG-CoA reductase inhibitor. Animal models have demonstrated the role of Pravastatin in reversing the imbalance in blood vessel growth that contributes to preeclampsia. It achieves this by increasing the production of PlGF and VEGF, while simultaneously inhibiting the production of sFlt-1 and sEng.[7,8] Furthermore, pravastatin enhances the flow of blood in the placenta and possesses features that reduce inflammation and prevent blood clotting. These characteristics make it a very promising drug to reduce the risk of placental-related disorders.[9-10] A recent RCT found that pravastatin was associated with a significantly reduced incidence of preterm preeclampsia ($p = 0.034$) and preterm birth ($p = 0.003$). [11] Nevertheless, there is a requirement for substantial proof as an alternative.[10] Hence, this study thoroughly investigated the effectiveness and safety of pravastatin in placental-related disorders. [12]

MATERIAL AND METHODS

Ethical statement

Due to the fact that this study solely involved the collection and analysis of secondary data from published clinical studies, ethical approval was deemed unnecessary.

Search Strategy

This study was registered with PROSPERO (CRD42024576331) and was conducted based on PRISMA criteria. The search was performed in PubMed, Cochrane Library, and CNKI until July 1, 2024. The keywords employed were statin, pravastatin, placental-related disorders, placental insufficiency, placental abnormalities, and preeclampsia. We imposed no limitations on the languages used and only considered studies involving human participants.

Study criteria

The studies utilized in our analysis were randomized controlled trials (RCTs) that satisfied the PICOS criteria. The participants consisted of pregnant women, the intervention involved the use of pravastatin, and the comparison groups received either a placebo or standard prophylaxis (aspirin + calcium). The outcomes assessed included maternal and neonatal outcomes, as well as adverse events. All of the included studies followed a RCT design. We removed all non-RCT studies from the sample.

Two writers (GAS and AP) conducted a thorough and independent review of the literature by initially screening titles and abstracts, and subsequently examining the entire texts to determine their suitability. A third researcher arbitrated any discrepancies in the literature search. The data was retrieved and condensed into a standardized format, comprising the study details, year, country, sample size, gestational age, administered dose, and findings.

Quality assessment

The study was evaluated by the first and second authors using the Cochrane RoB tool. Study quality was divided into high, moderate, and low risk.[13,14] Any disagreement between

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researchers was resolved by involving a third researcher.

Statistical Analysis

The application we used in this study was RevMan version 5.3. Chi-square (Chi^2) and I^2 tests were used to assess heterogeneity at the 0.1 and 50% levels. In the results of $I^2 < 50\%$ and $Chi^2 > 0.1$, we used a fixed effect model. If there was a difference between the two, the Chi^2 test results followed I^2. We use the Mantel-Haenszel model on dichotomous data. Furthermore, OR (odds ratio) effect size was used to determine the 95% confidence interval (CI).[15-19]

RESULT

Search results

We conducted a comprehensive search of the PubMed (67,773), Cochrane Library (36), and CNKI (3) databases, yielding a total of 67,812 publications that are pertinent to the specified keywords. After conducting an initial screening process that involved eliminating duplicate articles, inappropriate study designs, and full-text articles, a total of about 825 articles were identified. In the last stage, we eliminated 6 articles because they made unsuitable comparisons [20] and had unsatisfactory outcomes. [21] In addition, we incorporated three studies that had been previously examined.[11,21,22] This study incorporates a quantitative synthesis of six randomized controlled trial (RCT) research articles, which were published between 2016 and 2022.[11,22-26] This study incorporated 5 articles that compared pravastatin with placebo [11,22-25], as well as 1 article that compared pravastatin with conventional prophylaxis.[26] Figure 1 is the flowchart illustrating the selection method employed in this investigation.

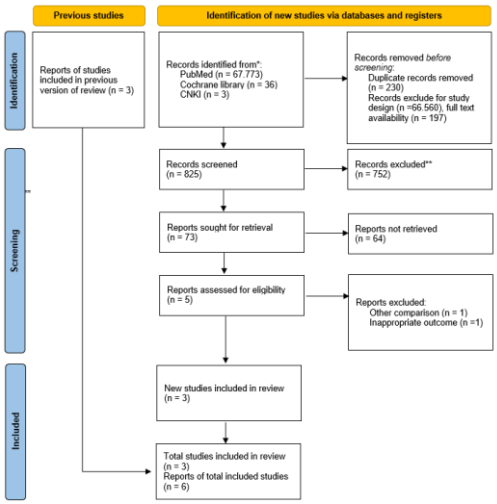

Figure 1. Search process flowchart.

Study characteristics

There were 6 RCT studies that examined a total of 1728 persons. The sample sizes in these trials varied from 10 to 548, while the gestational ages of the participants ranged from 12 to 41 weeks. Table 1 presents the overall attributes of the RCTs that were used in this investigation.

Quality assessment

Figure 2 displays the outcomes of the risk of bias evaluation for the 6 randomized controlled trials (RCTs). The 6 investigations provided sufficient information on random sequence generation, selective reporting details, and other biases.[11,22-24,] One study failed to mention the implementation of blinding for both subjects and investigators.[25] Four research provided specific information regarding allocation concealment.[11,22-24,26]

Tabel 1. Baseline characteristics of studies.

Study (year)	Country	Sample		Pregnancy age (weeks)	Dose		Finding
		I	C		I	C	
Akbar et al (2022)	Indonesia	87	86	14-20	Pravastatin 2x20 mg	Aspirin 1x80 mg + calcium 1x1 g	Pravastatin, taken at a dosage of 2x20 mg, effectively decreases the likelihood of experiencing early preeclampsia and preterm

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						birth.
Constatine et al (2021)	US	10	12-16	Pravastatin 1x20 mg	Placebo	This study confirmed the overall safety of pravastatin and its beneficial effects on pregnancy outcomes in women who are at a high risk of developing preeclampsia.
Döbert et al (2021)	England, Spain, and Belgium	548	35/36/37-41	Pravastatin 2x20 mg	Placebo	Administering pravastatin at a dosage of 20 mg per day from 35 to 37 weeks of pregnancy until delivery did not decrease the occurrence of preeclampsia in women with high-risk pregnancies with a single fetus.
Ahmed et al (2019)	United Kingdom	30	24-31 + 6 days	Pravastatin 1x40 mg	Placebo	Pravastatin is not effective in treating preeclampsia. However, no significant complications were found.
Hassanain et al (2018)	Egypt	200	13-16	Pravastatin 1x10 mg	Placebo	During the neonatal period, pravastatin can effectively prevent preeclampsia in newborns, including fetal weight, gestational age at delivery, and NICU admission.
Constatine et al (2016)	US	11	12-16 + 6 days	Pravastatin 1x10 mg	Placebo	No safety hazards were found in relation to the usage of pravastatin in this investigation.

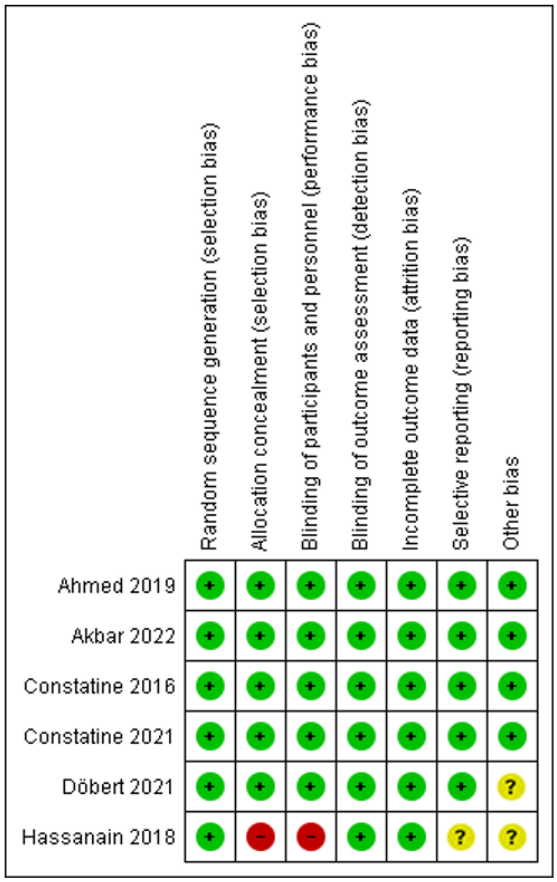

Figure 2. Risk of bias assessment

One study failed to provide information regarding the concealment of outcomes.[25] The 4 studies presented sufficient information regarding blinding to participants, investigators, and outcome assessors, and were classified as having low bias. [11,22-24,26]

Maternal outcomes

Four studies involving 614 participants investigated the risk reduction of preeclampsia. The number of preeclampsia cases was the final parameter considered. There was significant variation between groups, with an OR of 0.35 and a 95% CL of 0.20 to 0.62. The heterogeneity between the studies was 0% (Figure 3).

One study that examined the effects of pravastatin on reducing the risk of preeclampsia did not consider the trial because patients in the study already had hypertension before receiving the drug. [26]

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However, this study was included in other meta-analyses because it had little bias. Three trials, totaling 214 participants, discovered a significant difference in preterm birth rates between the intervention and control groups (OR: 0.34; 95% CL: 0.18-0.66; I^2: 29%) (Figure 4).

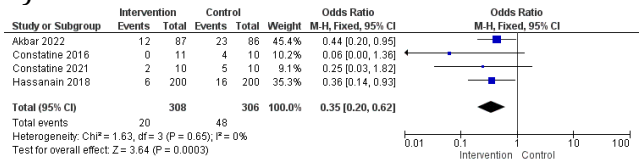

Figure 3. The demonstration of the effect of pravastatin administration on the risk of

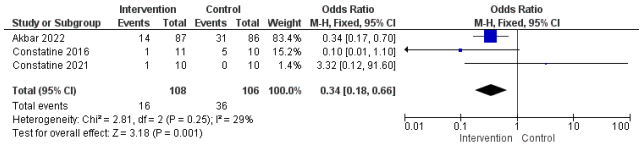

Figure 4. The demonstration of the effect of pravastatin administration on the risk of preterm birth.

Neonatal outcomes

In a meta-analysis of four studies featuring a total of 1194 participants, a significant disparity was observed between the intervention and control groups in terms of the number of neonates admitted to the NICU (Figure 5). The OR was 0.52, and the 95% CI ran from 0.28 to 0.97. The heterogeneity (I^2) was 0%. In the field of infant respiratory distress syndrome, a meta-analysis of three studies with a total of 1174 participants demonstrated this (OR: 0.66; 95% CL: 0.35–1.23; I2: 3%) (Figure 6). There was no significant variation between groups. After analyzing four studies with a total of 1573 participants, it was determined that there was no significant variation between groups in terms of congenital abnormalities (OR: 0.65; 95% CL: 0.26–1.66; I^2: 8%) (Figure 7).

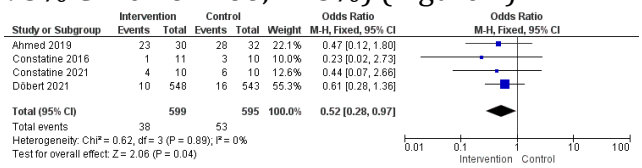

Figure 5. The demonstration of the effect of pravastatin administration on the risk of NICU admissions.

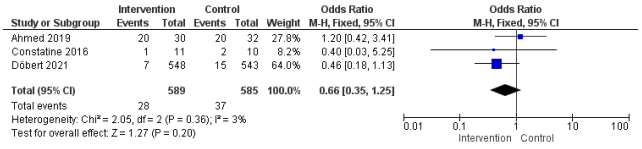

Figure 6. The effect of pravastatin administration on the risk of neonatal respiratory distress syndrome

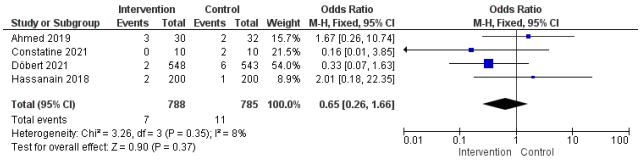

Figure 7. The effect of pravastatin administration on the risk of congenital abnormalities in neonates.

Adverse events

There were 6 RCT studies that examined a total of 1728 persons. The prevalence of headache (OR: 0.82; 95% CI: 0.27–2.48), epigastric pain (OR: 1.80; 95% CI: 0.58–5.55), and musculoskeletal pain (OR: 1.25; 95% CI: 0.46–3.37) did not show any significant variation between the groups. The results showed no variation observed among the studies in terms of headache (Chi²: 2.06; I^2: 3%), epigastric pain (Chi²: 1.39; I^2: 0%), and musculoskeletal pain (Chi²: 1.84; I2: 0%) (Fig. 8-10).[4,8,9]

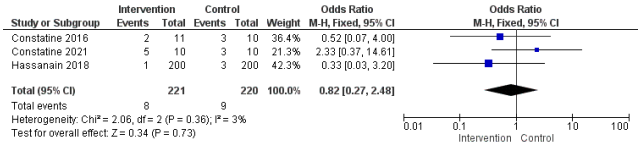

Figure 8. The demonstration of pravastatin administration on the risk of headache

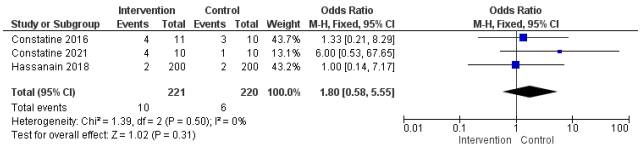

Figure 9. The demonstration of pravastatin administration on the risk of heartburn

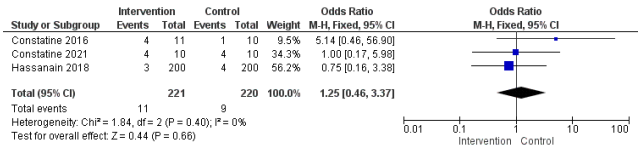

Figure 10. The demonstration of pravastatin administration on the risk of musculoskeletal pain

DISCUSSION

Placental-related disorders show connections with cardiovascular diseases.

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Both conditions are linked to inflammation, oxidative stress, and damage to the endothelium cells. Placental diseases, such as preeclampsia, intrauterine growth restriction (IUGR), placental abruption, and placenta accreta, impact around one-third of pregnancies. These abnormalities can result in significant rates of maternal and fetal death and illness.[27-29] Given the similarities between placental problems and cardiovascular diseases, it is possible that medications used to treat cardiovascular diseases could be advantageous for women who are at risk of developing placental disorders.[30-31] Currently, aspirin is advised for high-risk women to decrease the likelihood of recurrence, particularly in relation to preeclampsia.[32] Prior research has indicated that pravastatin can be utilized as a preventive measure against preeclampsia.[32] Nevertheless, there is ongoing debate regarding its effectiveness and safety. Thus far, evidence-based medicine has proven inadequate in tackling this matter.[33] Hence, it is crucial to investigate the effectiveness and safety of pravastatin.[35-36] It provides a summary of the available clinical evidence regarding the effectiveness and safety of pravastatin in reducing the risk of preeclampsia and improving maternal and neonatal outcomes.[37]

This analysis comprised six RCTs, which examined a combined sample size of 1728 people. A detailed and systematic comparison was made between the effectiveness and safety of pravastatin and the control group, which consisted of either a placebo or a combination of aspirin and calcium. The results of this study indicate that administering pravastatin is linked to a notable decrease in the occurrence of preeclampsia, preterm delivery, and admission to the NICU. However, it does not have an effect on the frequency of neonatal respiratory illnesses and congenital abnormalities. These findings indicate that pravastatin may have positive effects in pregnant women.[38-39]Administration of pravastatin did not result in any notable adverse effects, such as headache, heartburn, and musculoskeletal pain.[40-43]

Pravastatin's capacity to increase the production of nitric oxide in blood vessels, thereby fostering the generation of angiogenic growth factors, is the primary factor contributing to its beneficial effect on pregnancy.[44-46] The severity of preeclampsia, negative pregnancy outcomes, and a shortened duration of pregnancy are all associated with higher levels of angiogenic factors.[47-49] Statins have been shown to increase the synthesis of Th^2 anti-inflammatory cytokines and decrease the production of Th^1 inflammatory cytokines, thereby exhibiting anti-inflammatory abilities. In contrast to the control group, the pravastatin group exhibited lower serum interleukin (IL)-6 levels (inflammatory cytokines).[50-53] This is corroborated by the data.

This study is subject to several limitations. Firstly, there is a possibility that several potential studies were not included in this study. Secondly, the number of randomized controlled trials (RCTs) related to pravastatin in placental disorders is very limited. Thirdly, the study did not report long-term follow-up after delivery. Lastly, there was a lack of data collected to analyze the side effects that emerged during the study.

Additional clinical trials involving larger numbers of participants are required to fully assess the efficacy of pravastatin as a pharmaceutical intervention to reduce placental-related disorders. Further research is needed to determine the optimal dosage, timing, and duration for administering pravastatin. Even though there does not seem to be a risk of fetal deformity, long-term follow-up studies are necessary before pravastatin usage in pregnancy is widely recommended.

CONCLUSION

This study suggests that pravastatin use may have beneficial effects in reducing the risk of placental-related disorders (preeclampsia, preterm birth, and NICU admission) in

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patients. However, to support this conclusion, it is important to conduct extensive, well-planned, and adequately powered randomised controlled trials.

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DECLARATIONS

GAS, AP and NPS designed the study and collected data and prepared the manuscript, MVS reviewed the manuscript. The final manuscript was approved by all authors.

REFERENCES

1. ACOG Practice Bulletins. Clinical management guidelines for obstetrician- gynecologists. Obstetrics Gynecol. 2020; 133 (76), 168-186.
2. Karrar SA, Martingano DJ, Hong PL. Preeclampsia. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570611/
3. Perkumpulan Obstetri dan Ginekologi Indonesia Himpunan Kedokteran Feto Maternal. Pedoman Nasional Pelayanan Kedokteran: Diagnosis dan Tatalaksana Preeklampsia. 2016. Available from: https://www.pogi.or.id/wp-content/uploads/download-manager-files/PNPK%20PreEklampsia%202016.pdf
4. Marrs CC, Costantine MM. Should We Add Pravastatin to Aspirin for Preeclampsia Prevention in High-risk Women? Clin Obstet Gynecol. 2017;60(1):161-168. https://doi.org/10.1097/GRF.0000000000000248
5. Fox R, Kitt J, Leeson P, et al. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. J Clin Med. 2019 Oct 4;8 (10):1625. https://doi.org/10.3390/jcm8101625
6. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: Meta-analysis of randomised controlled trials. BMJ. 2009; 339 (7711): b2376. https://doi.org/10.1136/bmj.b2376
7. Costantine MM. Long-term child follow-up of the pravastatin for prevention of preeclampsia pilot trials. Am. J. Obstet. Gynecol. 2022; 226 (1): S74-S75. https://doi.org/10.1016/j.ajog.2021.11.142
8. McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: A cohort studyusing thegeneral practice research database to investigate pregnancy loss. Pharmacoepidemiol. Drug Saf. 2017; 26 (7): 843-852. https://doi.org/10.1002/pds.4176
9. Lefkou E, Varoudi K, Pombo J, et al. Triple therapy with pravastatin, low molecular weight heparin and low dose aspirin improves placental haemodynamics and pregnancy outcomes in obstetric antiphospholipid syndrome in mice and women through a nitric oxide-dependent mechanism. Biochem. Pharmacol. 2020; 182: 114217 https://doi.org/10.1016/j.bcp.2020.114217
10. Lefkou E, Mamopoulos A, Dagklis T, et al. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J. Clin. Invest. 2016; 126 (8), 2933-2940. https://doi.org/10.1172/JCI86957
11. Akbar MIA, Aziz MA, Riu DS, et al. INOVASIA study: A multicenter randomized clinical trial of pravastatin to prevent preeclampsia in high risk patients. Am J Perinatol. 2022. https://doi.org/10.1055/a-1798-1925
12. Higgins J, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. London: Cochrane. 2022.
13. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: Cohort study. BMJ. 2015; 350, h1035. https://doi.org/10.1136/bmj.h1035
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2020; 372: n71-1. https://doi.org/10.1136/bmj.n71
15. Russo MW. How to Review a Meta-analysis. Gastroenterol Hepatol (N Y). 2007 Aug; 3(8): 637-42.
16. Harrer M, Cuijpers P, Furukawa TA, et al. Doing meta-analysis with R: ahands-on guide. 1st ed. Boca Raton, FL: Chapman & Hall. 2021. https://doi.org/10.1201/9781003107347
17. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002. 21:1539-58. https://doi.org/10.1002/sim.1186
18. Core R, Team R. a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. 2022
19. Schwarzer G. Meta: general package for meta-analysis. Cham: Springer. 2022. https://doi.org/10.1002/9781119099369.ch26
20. Akbar M, Yosediputra A, Pratama R, et al. INOVASIA study: a randomized open controlled trial to evaluate pravastatin to prevent preeclampsia and its effects on sFlt1/PlGF levels. Am J Perinatol. 2021. https://doi.org/10.1055/a-1673-5603
21. Deviana SR, Sunarno I, Lukas E, et al. The effect of pravastatin on endothelin-1 levels and pregnancy outcomes in women who have a high risk for preeclampsia: A randomized control trial. Enferm. Clin. 2020; 30, 499-505. https://doi.org/10.1016/j.enfcli.2019.07.147

22. Costantine MM, West H, Wisner KL, et al. A randomized pilot clinical trial of pravastatin versus placebo in pregnant patients at high risk of preeclampsia. Am. J. Obstet. Gynecol. 2021;225(6):666.e1-666.e15. https://doi.org/10.1016/j.ajog.2021.05.018
23. Ahmed A, Williams DJ, Cheed V, et al. Pravastatin for early-onset pre-eclampsia: A randomised, blinded, placebo-controlled trial. BJOG. 2020; 127: 478 488. https://doi.org/10.1111/1471-0528.16013
24. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: A pilot randomized controlled trial. Am.J.Obstet.Gynecol. 2016; 214 (6), e1-e720. doi:10.1016/j.ajog.2015. 12.038 https://doi.org/10.1016/j.ajog.2015.12.038
25. Hassanain MS, Abdel-Aziz BR, Elsayed MA. Effect of pravastatin on the incidence of preeclampsia. Egypt J Hosp Med. 2018; 73: 7104-7111. https://doi.org/10.21608/ejhm.2018.17508
26. Dobert M, Varouxaki AN, Mu AC, et al. Pravastatin versus placebo in pregnancies at high risk of term preeclampsia. Circulation. 2021;144: 670-679. https://doi.org/10.1161/CIRCULATIONAHA.121.053963
27. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343 (7829): d5928-d5929. https://doi.org/10.1136/bmj.d5928
28. Wójtowicz A, Zembala-szczerba M, Babczyk D, et al. Early and late onset preeclampsia: A comprehensive cohort study of Laboratory and Clinical Findings according to the New ISHHP Criteria. Int J Hypertens. 2019: 4108271. https://doi.org/10.1155/2019/4108271
29. Ananth C, Keyes K, Wapner R. Pre-eclampsia rates in the United States, 1980-2010:age-period-cohort analysis. BMJ. 2013; 347:f6564. https://doi.org/10.1136/bmj.f6564
30. Mendoza M, Ferrer-Oliveras R, Bonacina E, et al. Evaluating the effect of pravastatin in early-onset fetal growth restriction: A nonrandomized and historically controlled pilot study. Am. J. Perinatol. 2020; 1 (212), 1472-1479 https://doi.org/10.1055/s-0040-1713651
31. Pollack PS, Shields KE, Burnett DM, et al. Pregnancy outcomes after maternal exposure to simvastatin andlovastatin. Birth Defects Res. A Clin. Mol. Teratol. 2005; 73 (11): 888-896. https://doi.org/10.1002/bdra.20181
32. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2021; 72:24-43. https://doi.org/10.1161/HYPERTENSIONAHA.117.10803
33. Brown M, Magee L, Kenny L, et al. International society for the study of hypertension in pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018; 72:24-43. https://doi.org/10.1161/HYPERTENSIONAHA.117.10803
34. Steegers E, von Dadelszen P, Duvekot J, et al. Lancet. 2010; 376:631-44 https://doi.org/10.1016/S0140-6736(10)60279-6
35. Ishimwe J. Maternal microbiome in preeclampsia pathophysiology and implicationson offspring health. Physiol Rep. 2021; 9:e14875. https://doi.org/10.14814/phy2.14875
36. Ma'ayeh M, Rood K, Kniss D, et al. Novel interventions for the prevention of preeclampsia. Curr Hypertens Rep. 2020; 22:17. https://doi.org/10.1007/s11906-020-1026-8\
37. Gajzlerska-Majewska W, Bomba-Opon D, Wielgos M. Is pravastatin a milestone inthe prevention and treatment of preeclampsia? J Perinat Med. 2018; 46:825-31. https://doi.org/10.1515/jpm-2017-0109
38. Dymara-Konopka W, Laskowska M, Bła˙zewicz A. Angiogenic imbalance as acontributor of preeclampsia. Curr Pharm Biotechnol. 2018; 19:797-815. https://doi.org/10.2174/1389201019666180925115559
39. Knapp G, Hartung J. Improved tests for a random effects meta-regression with asingle covariate. Stat Med. 2003; 22:2693-710. https://doi.org/10.1002/sim.1482
40. Sweeting M, Sutton A, Lambert P. What to add to nothing? use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004; 23:1351-75. https://doi.org/10.1002/sim.1761
41. IntHout J, Ioannidis J, Borm G. The hartung-knapp-sidik-jonkman method for random effects meta-analysis is straight forward and considerably out performs the standard dersimonian-laird method. BMC Med Res Methodol. 2014; 14:25. https://doi.org/10.1186/1471-2288-14-25
42. Xu T, Zhou F, Deng C, et al. Low-dose aspirin for preventingpreeclampsia and its complications: a meta-analysis. J Clin Hypertens. 2015; 17:567-73. https://doi.org/10.1111/jch.12541
43. Mészáros B, Veres DS, Nagyistók L, et al. Pravastatin in preeclampsia: A meta-analysis and systematic review. Front Med (Lausanne). 2023 Jan 13;9:1076372. https://doi.org/10.3389/fmed.2022.1076372
44. Hirsch A, Rotem R, Ternovsky N, et al. Pravastatin and placental insufficiency associated disorders: A systematic review and meta-analysis. Front Pharmacol. 2022; Nov 9;13:1021548. https://doi.org/10.3389/fphar.2022.1021548

45. Meijerink L, Wever KE, Terstappen F, et al. Statins in pre-eclampsia or fetal growth restriction: A systematic review and meta-analysis on maternal blood pressure and fetal growth across species. BJOG. 2023; May;130(6):577-585. https://doi.org/10.1111/1471-0528.17393
46. Zarek J, Koren G. The fetal safety of statins: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2014 Jun; 36(6):506-509. https://doi.org/10.1016/S1701-2163(15)30565-X
47. Burton G, Redman C, Roberts J, Moffett A. Pre-eclampsia: pathophysiology andclinical implications. BMJ. 2019; 366:l2381 https://doi.org/10.1136/bmj.l2381
48. Mikhailidis D, Athyros V. Dyslipidaemia in 2013: new statin guidelines andpromising novel therapeutics. Nat Rev Cardiol. 2014; 11:72-4. https://doi.org/10.1038/nrcardio.2013.209
49. Smith D, Costantine M. The role of statins in the prevention of preeclampsia. Am JObstet Gynecol. 2022; 226:S1171-81. https://doi.org/10.1016/j.ajog.2020.08.040
50. Smith DD, Costantine MM. The role of statins in the prevention of preeclampsia. Am J Obstet Gynecol. 2022; 226: S1171 S1181 https://doi.org/10.1016/j.ajog.2020.08.040
51. Staff AC, Redman CWG. Comprehensive Gynecology and Obstetrics: The Differences Between Early- and Late-Onset Pre-eclampsia. Singapore: Springer Nature. pp. 2018; 157-172. https://doi.org/10.1007/978-981-10-5891-2_10