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TABLE OF CONTENTS

[Intervention Protocol]

Statins for preventing preeclampsia

Themistoklis Paraskevas[1], Georgios Gakis[2], Michail Papapanou[3], Theodoros N Sergentanis[4], Alexandros Sotiriadis[5], Charalampos S Siristatidis[6]

[1]Department of Nephrology, General University Hospital of Patras, Patras, Greece. [2]General University Hospital of Patras, University of Patras, Patras, Greece. [3]Second Department of Obstetrics and Gynecology, Aretaieion University Hospital, National and Kapodistrian University of Athens, Athens, Greece. [4]Department of Public Health Policy, School of Public Health, University of West Attica, Athens, Greece. [5]Second Department of Obstetrics and Gynaecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. [6]Assisted Reproduction Unit, Second Department of Obstetrics and Gynaecology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Contact: Themistoklis Paraskevas, themispara@hotmail.com.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the relative benefits and harms of statins for preeclampsia prevention in pregnant women.

BACKGROUND

Description of the condition

Preeclampsia, which belongs to the hypertensive disorders of pregnancy, is defined as new-onset hypertension plus proteinuria or systemic manifestations detected after 20 gestational weeks [1]. Diagnosis can be made if women present with new-onset hypertension in the second trimester (> 20 weeks of gestation) and proteinuria, or without proteinuria and one or more of the following: thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new-onset headache unresponsive to medication [2, 3]. The worldwide incidence of preeclampsia ranges from 2% to 10% according to the World Health Organization (WHO) [4]. The exact pathophysiology of the disease has not yet been determined. Traditionally, preeclampsia has been considered a primarily placental disease, resulting from the inadequate transformation of the spiral arteries, which leads to an imbalance between pro- (prostaglandin I2 [PGI2], nitric oxide [NO], vascular endothelial growth factor [VEGF], and placental growth factor [PIGF]) and anti-angiogenic factors (soluble FMS-like tyrosine kinase-1 [sFlt-1], soluble endoglin [sEng], thromboxane A2, endothelin-1 [ET-1]) [5], and eventually endothelial dysfunction and placental ischemia [6]. Additionally, a dysregulated maternal-fetal immune tolerance [7], as well as genetic [8] and nutritional factors [9], have been implicated in the pathogenesis [5]. It has been recently proposed that subclinical maternal cardiovascular pathology precedes inadequate placentation ('maternal' origin of preeclampsia). The different degrees of placental involvement have been associated with the 'phenotype' of preeclampsia; heavier placental involvement has been associated with earlier onset and smaller fetuses ('early' or 'preterm' preeclampsia), while milder placental involvement has been linked with later onset and larger fetuses ('late' or 'term' preeclampsia) [10, 11]. Preeclampsia remains one of the major causes of maternal mortality [12] and is also linked with adverse fetal outcomes, such as preterm birth and fetal growth restriction [13]. To this day, no effective treatment other than the delivery of the fetus has been identified [14], thus highlighting the importance of prevention. The development of screening protocols [15] and the introduction of aspirin [16] have led to a reduction in early/preterm preeclampsia-related adverse outcomes. However, additional preventive measures are needed for term preeclampsia. While the prevention of preterm preeclampsia, especially before 34 and 32 weeks, has been quite effective, a similar effect has not been achieved for term preeclampsia [17].

Description of the intervention and how it might work

Statins are competitive inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis [18]. The resultant reduction in cholesterol synthesis induces an increase in the expression of hepatic low-density lipoprotein (LDL) receptors (LDL-R), which leads to an increased uptake of LDL cholesterol (LDL-C) and LDL precursors from the circulation [19]. Depending on the extent to which statins lower LDL-C levels, they are categorized into three groups: low-intensity statins lower LDL-C by < 30%; moderate-intensity statins lower LDL-C levels by 30% to < 50%; and high-intensity statins lower LDL-C levels by ≥ 50% [20]. For example, pravastatin at a dose of 10 or 20 mg, simvastatin at 20 to 40 mg, and atorvastatin at 40 mg are considered low-, medium-, and high-intensity statin therapies, respectively. Statins exert their main pharmacological actions through the halt of the atherosclerosis process and the reduction of vascular smooth muscle cell hypertrophy and hyperplasia, deposition of fibrin, and protein cross-linking [21]. As such, they can lead to a reduction of major atherosclerotic cardiovascular disease (ASCVD) events [22] and are considered the first-line pharmacological treatment in dyslipidemia management [23]. Despite their well-established beneficial actions, statins are linked to a variety of adverse effects, with the most serious being myalgia, statin-induced myopathy with potential resultant rhabdomyolysis, and derangement in liver function tests [24]. Statins have also been implicated in a variety of drug-to-drug interactions, which should always be considered to ensure patient safety [25]. Pravastatin, in particular, is a potentially trustworthy option for preeclampsia prevention with a favorable safety profile and no reports of congenital anomalies [26]. Current systematic reviews have concluded that pravastatin lowers blood total cholesterol, LDL cholesterol, and triglyceride in a dose-dependent linear fashion, without providing a good estimate of the incidence of harms associated with its use because of the lack of reporting of adverse effects in half of the included randomized controlled trials [27]. In contrast, another systematic review failed to demonstrate any benefit for preventing preeclampsia in high-risk pregnant women, as the findings came only from preliminary studies with a small number of participants [28].

Recent reports have identified statins, especially pravastatin, as a promising option for preeclampsia prevention, either as a monotherapy [29] or in combination with other pharmacological therapies such as L-arginine [30]. The beneficial effects of pravastatin in addition to the established standard of care (low molecular weight heparin and low-dose aspirin) appear to be most pronounced in pregnant women diagnosed with antiphospholipid syndrome [31] [32]. This seems to be mediated through the reduction of endothelial dysfunction [33, 34], which, as previously stated, is among the main contributing factors to preeclampsia pathogenesis. Statin administration has also been associated with a reduction in the anti-angiogenic sFlt-1 levels [35, 36]. In a recent review of 12 studies, the authors showed that statins caused a significant dose-dependent decrease in sFlt-1 secretion from isolated cytotrophoblasts (sFlt-1 causes endothelial dysfunction by occupying the PIGF receptor, which causes the reduction of PIGF), increased secretion of sEng (at least in some studies) in placental explants obtained from women with preeclampsia, and increased endothelial nitric oxide synthase (eNOS) in preeclamptic placentas [37]. Also, statins were beneficial for women with APS by preventing preeclampsia, and might reduce the complications of Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome [37]. Among the proposed mechanisms of their protective role in preeclampsia are the reversal of the pregnancy-specific imbalance and oxidative and inflammatory stress, the improvement of the endothelial function as stated above, the reduction of the expression of adhesive molecules such as VCAM-1 and endothelin-1 on endothelial cells, and the enhancement of endothelial cells migration and invasion [37, 38]. Notably, there is growing evidence of the association between maternal cardiovascular health and cardiovascular dysfunction and disease in the newborn; the former leads to a pro-inflammatory environment and an adverse maternal environment from preconception onwards, which can negatively affect gametogenesis and endometrial quality and lead to placental, embryonic, and fetal structural and functional developmental adaptations [39].

Statins have been linked to adverse fetal outcomes, such as low birthweight, preterm birth, and lower 1-minute Apgar score [40, 41]; however, some clinical trials do not seem to confirm these findings [31, 36]. In addition, statin administration during pregnancy has traditionally been contraindicated due to theoretical concerns about their teratogenicity. However, evidence has shown that statin exposure is not associated with birth defects [42]. Pharmacokinetic studies also did not identify any high-risk pharmacokinetic profile for pregnant women [43]. In addition, the US Food and Drug Administration (FDA) has recently suggested that their continuation could benefit certain high-risk pregnancies [44]. A careful assessment of the possible role of statins in preeclampsia prevention is thus needed.

Why it is important to do this review

Our question is relevant to pregnant women and newborns, populations where drug approval is much more regulated and strict because of possible adverse outcomes [45]. As of the time of writing, no effective pharmacological preventive interventions other than aspirin are available [46], resulting in a need for novel and effective therapeutic or preventive pharmacological interventions [47]. Although promising alternatives have been proposed [48], and randomized controlled trials regarding statin efficacy in preeclampsia prevention have been published [49], we are not aware of a methodologically complete systematic review on the matter that can be used to inform clinical practice, leading to robust answers. We aim to complement the published literature by holistically presenting efficacy and safety data and following standard Cochrane methods.

If this cheap and easily available class of drugs is proven effective [50], statins could aid in the reduction of the increased economic burden associated with adverse preeclampsia outcomes, such as the need for hospitalization or admission to the intensive care unit (ICU) for both the mother and the fetus [51, 52]. Additionally, given that, according to the Preeclampsia Foundation, pregnant women in low and middle-income countries are seven times more likely to develop preeclampsia and are thus disproportionally affected compared to those in high-income countries [53, 54], statins could also aid in addressing issues of health equity regarding this condition.

OBJECTIVES

To evaluate the relative benefits and harms of statins for preeclampsia prevention in pregnant women.

METHODS

We will follow the methodology expected for Cochrane intervention reviews when conducting the review and the PRISMA 2020 Statement for the reporting [55]. We followed the guidance applicable to the Background and Methods sections to develop this protocol.

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomized controlled trials (RCTs) assessing the effectiveness and safety of statins for preventing preeclampsia in pregnancy. We will include cluster-RCTs and cross-over trials before cross-over, but we will exclude quasi-randomized or pseudo-randomized studies [56]. We will also include conference abstracts; we will contact the investigators for additional information about conduct or results as needed.

We will apply no restrictions regarding the year of dissemination or language.

Types of participants

We will include pregnant women at risk of developing preeclampsia. This will include women who are either normotensive or with pre-existing chronic hypertension, as well as those with gestational hypertension, regardless of preeclampsia history in previous pregnancies. We do not expect to find studies that only include a subset of participants eligible for inclusion. We will not apply any restrictions in terms of setting.

If applicable, we will classify pregnant women as being at high, moderate, or low clinical risk for developing preeclampsia according to the study authors. Should the authors use the 2020 ACOG Practice Bulletin on Gestational Hypertension and Preeclampsia [2], we will classify these groups as follows.

- Low risk for developing preeclampsia if they had one previous uncomplicated full-term delivery.
- Moderate risk for developing preeclampsia if they have one or more of the following risk factors:
  - nulliparity;
  - obesity (body mass index > 30 kg/m^2);
  - family history of preeclampsia (mother or sister);
  - African-American origin;
  - lower income;
  - age ≥ 35 years;
  - personal risk factors (low birthweight or small for gestational age, previous adverse pregnancy outcome, > 10-year pregnancy interval) or in vitro conception.
- High risk for developing preeclampsia if they have one or more of the following risk factors:
  - history of preeclampsia, especially when accompanied by an adverse outcome or multifetal gestation;
  - chronic hypertension;
  - pregestational type 1 or 2 diabetes;
  - kidney disease;
  - autoimmune disease (i.e. systemic lupus erythematosus, antiphospholipid syndrome);
  - combinations of multiple moderate-risk factors;
  - a high-risk result in combined tests including maternal and fetal factors.

Lastly, we will also classify pregnant women according to the gestational age at which preeclampsia is diagnosed, that is before or at/after 34^{+0} or 37^{+0} weeks of gestation.

Types of interventions

We will include any drug belonging to the statin drug family. We will apply no restrictions on statin dose (i.e. high or low) or intensity (i.e. high, intermediate, or low). To our knowledge, statins are administered orally, thus we do not expect to encounter alternative routes of administration.

- Statins versus standard care
- Statins versus standard care plus placebo
- Statins versus standard care plus an active intervention other than statins

We will further group statins as follows.

- High-intensity statins
- Moderate-intensity statins
- Low-intensity statins

We will not exclude studies based on the timing or duration of the intervention. We will further categorize interventions based on the timing of administration (before or after 16 weeks).

We will further group standard care as follows.

- Including aspirin
- Not including aspirin

Outcome measures

Critical outcomes

- The incidence of preeclampsia, defined either (a) as hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) and proteinuria (protein ≥ 300 mg in a 24-hour urine specimen or a protein/creatinine ratio of ≥ 0.3 or urine dipstick protein 1+ if quantitative measurement not available), detected for the first time after 20 weeks of gestation; or (b) according to the updated definitions by the American College of Obstetricians and Gynecologists (ACOG) [2] and the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute for Health and Care Excellence (NICE) [57].
- Small for gestational age (SGA), defined as estimated fetal weight/birthweight below the 10th percentile (after 20 weeks of gestation) [58].

We selected these critical outcomes according to the Core Outcome Measures in Effectiveness Trials (COMET) core outcome set for preeclampsia [59].

Table 1. Specific outcome measures for each outcome category

Broader outcome grouping	Outcome domain	Outcome measures
Maternal outcomes	Hypertensive disorders of pregnancy	Preeclampsia, preeclampsia with severe features, eclampsia
Newborn outcomes	Death	Perinatal death (defined as infant death occurring at less than 7 days of age and fetal death with a stated or presumed period of gestation of 28 weeks or more)
	Morbidity	SGA, preterm birth, statin-related congenital anomalies

Important outcomes

- Preeclampsia with severe features, as defined by the authors (after 20 weeks of gestation).
- Preterm birth (i.e. birth at less than 37 weeks of gestation).
- Perinatal death (defined as infant death that occurred at less than 7 days of age and fetal death with a stated or presumed period of gestation of 28 weeks or more).
- Eclampsia, which is a hypertensive disorder of pregnancy defined by new-onset tonic-clonic, focal, or multifocal seizures or unexplained altered mental status in a pregnant or postpartum patient in the absence of other causative etiologies (after 20 weeks of gestation) [60].
- Statin-related congenital anomalies, defined as evident before birth or within the first year of life.

If we exclude studies on the basis of outcomes, care will be taken to ascertain that relevant outcomes are not available because they have not been measured rather than simply not reported.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases for relevant trials:

- Cochrane Central Register of Controlled Trials (CENTRAL) (now containing output from the ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform [ICTRP] trial registries and CINAHL [Cumulative Index to Nursing and Allied Health Literature]), via the Cochrane Register of Studies Online (CRSO), Web platform, from inception onwards;
- MEDLINE (Epub Ahead of Print, In Process and Other Non-Indexed Citations), Ovid platform, searched from 1946 to present; and
- Embase, Ovid platform, searched from 1980 to present.

The MEDLINE search will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials [61]. The Embase search will be combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/what-we-do/methodology/search-filters/).

We will not impose any language or date restrictions on our search algorithm. An example of the MEDLINE search strategy can be found in the Appendix (Supplementary material 1).

Searching other resources

We will examine the reference lists of the retrieved studies, relevant reviews, and conference proceedings of major conferences (e.g. ACOG, RCOG, European Board & College of Obstetrics and Gynaecology [EBCOG], European Society of Gynecology [ESG]) for additional references. We will search relevant grey literature sources for additional studies, such as the Google Scholar database (first 200 records). We will search the Epistemonikos database (www.epistemonikos.org/), a multilingual database of health evidence and the largest source of systematic reviews. We will consult experts in the field for ongoing or existing studies.

Data collection and analysis

Selection of studies

Two review authors (TP and GG) will independently screen the titles and abstracts of all articles retrieved from the searches according to the review inclusion criteria, excluding any studies that are clearly irrelevant. We will retrieve the full-text versions of the remaining potentially eligible studies. Two review authors (TP and GG) will independently screen the full texts for inclusion in the review, listing the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table. Where eligibility of a study is unclear, we will contact the study authors for clarification as needed. Any disagreements between review authors will be resolved by discussion with a third review author (MP). We will translate any studies in a language other than those known by the review authors with the help of Cochrane and assess them for eligibility. We will use Covidence during screening [62]. We will summarize the study selection process in a PRISMA flow diagram.

Two review authors (TP and GG) will assess all studies meeting our inclusion criteria for trustworthiness according to the criteria described in Section 4.4.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* [61]. Specifically, we will use the Trustworthiness Screening Tool (TST) developed by the Cochrane Pregnancy and Childbirth Group [63]. We will apply the following predefined criteria to identify studies as sufficiently trustworthy for inclusion in the analysis, as per this tool.

- Research governance
  - No prospective trial registration for studies published after 2010 is available, without a plausible explanation.
  - Refusal of the trial authors to provide/share the protocol or ethics approval letter (or both) when requested.
  - Refusal of the trial authors to engage in communication with the Cochrane review authors.
  - Refusal of the trial authors to provide individual patient data upon request, with no justifiable reason.
- Baseline characteristics
  - Characteristics of the study participants are too similar (distributions of mean and standard deviation (SD) are excessively narrow or excessively wide) [64].
- Feasibility
  - Implausible numbers.
  - (Close to) zero losses to follow-up, without plausible explanation.
- Results
  - Implausible results.
  - Unexpectedly even numbers of participants 'randomized,' including a mismatch between the numbers and the methods (e.g. if it is stated that no blocking was used, but there are still equal numbers, or if it is stated that blocks of four were used, but the final numbers differ by six).

Where a study is classified as being at 'high risk' for one or more of the above criteria, we will attempt to contact the study authors twice to address any possible lack of information and concerns. If adequate information remains unavailable, we will categorize the study as awaiting classification and describe our concerns and communications with the author (or lack thereof) in detail [61].

Data extraction and management

Two review authors (TP and GG) will independently extract study characteristics and outcome data from the reports of each included study. Any disagreements between review authors will be resolved by discussion with a senior review author (MP or CSS).

We will extract data for all the above-mentioned critical and important maternal and neonatal outcomes according to the methodology described in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* [65].

Specifically, we will extract information about data extraction (names of data extractors, data extraction date, and identifiers for each report from which data are being extracted). We will also extract detailed information on participants (age, race, obstetric history, gestational week at randomization, preeclampsia diagnostic criteria, history of preeclampsia in previous pregnancy or pregnancies, comorbidities [hypertension, diabetes mellitus, chronic kidney disease, autoimmune diseases, and obesity], country/region, inclusion and exclusion criteria, and total number of participants screened and randomized), interventions (description of intervention and co-intervention[s], timing of administration, dose, duration, integrity of interventions, definition of control group[s] and number of participants assigned to each intervention group), outcomes (definition, time point of measurement, measurement tool or instrument[s] and results), study design (parallel or cluster and single- or multicenter, recruitment and sampling procedures, enrollment start and end dates, follow-up length, details on random sequence allocation and concealment and masking of participants), funding sources and declarations of interest of the primary investigators.

We will construct an appropriate data-centric Microsoft Excel file and pilot it on two eligible studies to identify any potential issues with this process. In the case of trials with multiple reports, we will use the main report as the reference and the secondary reports as supplementary [66]. If the published methodology or data require further clarification, we will contact the authors of the included studies via email.

Risk of bias assessment in included studies

Two review authors (TP and GG) will independently assess risk of bias in the included studies according to the methodology described in Chapters 7 and 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [67, 68]. A third review author (MP) will resolve any disagreements. We will use the Cochrane RoB 2 tool for RCTs and its variants for cluster-randomized trials and cross-over trials [69]. The RoB 2 tool assesses five domains where bias may arise: bias arising from the randomization process, bias

due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result [70].

We will judge each domain of bias as 'low risk of bias,' 'some concerns,' or 'high risk of bias' after answering the signaling questions in the RoB 2 tool [70], following the criteria outlined in the above-mentioned chapters of the *Cochrane Handbook* [67, 68]. We will support the answers with proper justification and quotations from the trial's text or registered protocol (or both) and will verify the judgments proposed by the tool's algorithms. The five domain-level judgments will provide the basis for the overall assessment. After consulting the algorithm's suggestions, we will reach an overall risk of bias judgment for each outcome of each study. We will judge trials at high risk of bias for the result if they are subject to high risk of bias in at least one domain or to some concerns in multiple domains unless we can justify a different judgment; low risk of bias if they are at low risk of bias for all domains; or some concerns if there are some concerns for at least one domain [67, 68, 70]. We may override this decision after the justification and consensus of the whole review team. In cases where study quality is unclear from trial protocols/publications, or if any questions arise, we will contact the principal investigators for clarification. We will implement the Excel tool for RoB 2 to efficiently store and present our judgments and their justifications (available from www.riskofbias.info/). This will be part of a separate document which we will make available with the review as an online supplemental file. For the domain 'bias due to deviations from intended interventions,' we are interested in the effect of assignment to intervention at baseline (intention-to-treat).

We will conduct a risk of bias assessment for the critical and important outcomes of our review (see Outcome measures), as follows.

- Preeclampsia incidence (after 20 weeks of gestation).
- SGA (after 20 weeks of gestation).
- Preeclampsia with severe features (after 20 weeks of gestation).
- Preterm birth (i.e. birth at less than 37 weeks of gestation).
- Perinatal death (defined as infant death that occurred at less than 7 days of age and fetal death with a stated or presumed period of gestation of 28 weeks or more).
- Eclampsia (after 20 weeks of gestation).
- Statin-related congenital anomalies, defined as evident before birth or within the first year of life.

Measures of treatment effect

For dichotomous data (e.g. preterm birth), we will use the numbers of events in the control and intervention groups of each study to calculate odds ratios (ORs). If required, we will reverse the direction of the effect of individual studies to ensure consistency across trials. We will present 95% confidence intervals (CIs) for all outcomes. We will consider a threshold of 1 in 500 events for our critical outcome of preeclampsia as trivial.

Unit of analysis issues

The unit of analysis will be the individual participant. For neonatal outcomes, the unit of analysis will be the newborn. If a single trial compares three or more arms (i.e. two or more treatment arms and one control arm), we will label the arms separately in pair-wise analyses. To avoid including data for controls more than once in the same comparison, we will divide the control group into equal parts while assuming equal incidence in these groups, or combine multiple treatment arms. We will also exclude irrelevant treatment arms from our analysis. Since the design of cross-over trials is not appropriate in this review's setting, we will only use data from the first phase of any such trials. For cluster-RCTs, we will extract the intracluster correlation coefficient (ICC) when available; we will also record the number of clusters per group, the total size of clusters per group, and the unit of randomization. If the ICC is not available, we will extract it from an RCT or an observational study with a similar population. If this is not possible, we will conduct a sensitivity analysis for different ranges of ICCs. We will combine the results of cluster-RCTs with the other RCTs only if their results are reasonably homogeneous.

Dealing with missing data

We will analyze data on an intention-to-treat basis to the greatest degree possible and attempt to obtain missing data from the study investigators.

We will seek missing information and clarification about the statistics presented by the authors as needed. We will email the authors of the included studies to retrieve additional data on key variables or methodological details where necessary. If we receive no response, we will send a reminder 20 days after the first communication.

Reporting bias assessment

Two review authors (TP and MP) will independently assess bias arising from missing evidence for our critical outcomes using the ROB-ME tool [71]. Any disagreements will be discussed between the two review authors or in consultation with the senior methodologist review author (TNS) when necessary.

We will assess reporting bias by comparing the planned critical and important outcomes (i.e. preeclampsia, SGA, preeclampsia with severe features, eclampsia, perinatal death, preterm birth, and statin-related congenital newborn anomalies) and the reported outcomes. In studies for which protocols are available, we will compare the protocol to the full publication to investigate possible reporting bias. In the case of missing results, we will contact the study authors to retrieve the additional data.

We will use funnel plots to screen for publication bias where a sufficient number of studies (more than 10) report the same outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this into our assessment of the certainty of the evidence [72]. However, if few studies are eligible for meta-analysis, the ability to detect publication bias will be largely diminished, and we will simply note our inability to rule out possible publication bias or small-study effects.

Synthesis methods

In our synthesis we will include studies of statin therapy with the following comparisons.

- Statins versus standard care
- Statins versus standard care plus placebo
- Statins versus standard care plus an active intervention other than statins

Given our strict inclusion and exclusion criteria, we do not plan to exclude any studies based on their PICOs (population, intervention, comparison, outcomes) from our synthesis. However, we will restrict our primary analysis to studies judged at low risk of bias based on their RoB 2 assessments for each outcome.

To tabulate our results, we will construct a table of study characteristics using data we collect during the data extraction process.

We will conduct pair-wise random-effects meta-analysis using RevMan software [73] based on the expected clinical heterogeneity (e.g. different baseline risks among included populations, differences in statin dosage and timing of administration, among others). We will conduct a meta-analysis only if the studies are sufficiently homogeneous regarding participants, interventions, and outcomes to provide a meaningful summary, according to Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [74]. If meta-analysis is not possible, we will follow Synthesis Without Meta-analysis (SWiM) guidance [75, 76]. We will estimate the between-study variation with a restricted maximum likelihood approach and calculate the CI for the summary effect using a Wald-type CI.

We will estimate heterogeneity variances for each pair-wise comparison in standard pair-wise meta-analyses and assess the presence of statistical heterogeneity by visually inspecting the forest plots and calculating the I^2 statistic [74]. An $I^2 > 50\%$ will be indicative of substantial heterogeneity.

Investigation of heterogeneity and subgroup analysis

We will conduct subgroup analyses to investigate potential heterogeneity in the critical and important outcomes of our review (preeclampsia incidence, SGA, preeclampsia with severe features, preterm birth, perinatal death, eclampsia, and statin-related congenital newborn anomalies). Due to the nature of the outcomes, we will prioritize different time points for each one, as described in the Outcome measures section. We will assess all subgroup analyses using the formal test for subgroup differences in RevMan. In the event of fewer than five studies in each subgroup, we will not highlight the findings, as they are unlikely to be adequate for a meaningful analysis. We plan to carry out subgroup analyses of the following factors that may contribute to heterogeneity in the effects of the intervention:

- number of fetuses (i.e. singleton versus multiple pregnancy);
- intensity of statin therapy;
- inclusion or not of aspirin in background therapy;
- timing of administration (before or after 16 weeks);
- country's income per the World Bank's definition.

Equity-related assessment

We plan to conduct separate analyses in studies reporting data from low- or middle-income countries as defined by the 2023 World Bank Country Classification by Income Level [77]. We chose this population due to the high risk of preeclampsia and associated morbidity [54].

Sensitivity analysis

Our primary analysis will be restricted to studies judged at an overall low risk of bias. We will conduct a sensitivity analysis for the critical and important outcomes of our review (preeclampsia, SGA, preeclampsia with severe features, preterm birth, perinatal death, eclampsia, and statin-related congenital newborn anomalies) including studies with some concerns and high risk of bias. Given the nature of the outcomes, we will prioritize different time points for each one, as described in the Outcome measures section.

Additionally, we will investigate if the findings are different if:

- the onset of preeclampsia differs. According to onset, preeclampsia can be defined as:
  - preterm preeclampsia (preeclampsia before 37 weeks);
  - term preeclampsia (preeclampsia at or after 37 weeks);
  - early preeclampsia (preeclampsia before 34 weeks);
  - late preeclampsia (preeclampsia at or after 34 weeks), which includes postpartum preeclampsia.
- the summary effect measure is risk ratio (RR) rather than OR;
- the study's source differs (i.e. full text or only an abstract is available);
- individuals with a high risk of preeclampsia (as defined by the study authors) are only included; and
- individuals with a high risk of preeclampsia (as defined by combined screening models) are only included.

Certainty of the evidence assessment

We will create a summary of findings table using GRADEpro GDT software [78] and the *Cochrane Handbook for Systematic Reviews of Interventions* for each of the following comparisons.

- Statins versus standard care
- Statins versus standard care plus placebo
- Statins versus standard care with an active intervention other than statins

We will evaluate the overall certainty of the evidence for the critical and important outcomes of our review [78, 79, 80], as follows.

- Preeclampsia incidence (after 20 weeks of gestation).
- SGA (after 20 weeks of gestation).
- Preeclampsia with severe features (after 20 weeks of gestation).
- Preterm birth (i.e. birth at less than 37 weeks of gestation).
- Perinatal death (defined as infant death that occurred at less than 7 days of age and fetal death with a stated or presumed period of gestation of 28 weeks or more).
- Eclampsia (after 20 weeks of gestation).
- Statin-related congenital anomalies, defined as evident before birth or within the first year of life.

Two review authors (TP and GG) will independently use the GRADE approach to assess the certainty of evidence as high, moderate, low, or very low based on the five considerations (i.e. overall risk of bias, inconsistency, imprecision, indirectness, and publication bias) for potential downgrading and three considerations (i.e. large effects, dose-response, and opposing plausible confounding) for potential upgrading. Any disagreements will be resolved through discussion with another review author (MP). Regarding the overall risk of bias criterion, the overall RoB 2 judgment for the result of each outcome will inform the GRADE assessment. We will justify, document, and incorporate judgments about the certainty of evidence into reporting the results for each outcome. We will use the definitions

for each level of certainty as described in Chapter 5 of the GRADE Handbook [79].

Based on GRADE guidance 34 [81], we will follow a minimally contextualized approach to assess imprecision. For our critical outcome of preeclampsia, we will consider a trivial threshold of 1 in 500 events. When the CI does not cross this threshold, we will calculate and consider the optimal information size (OIS) for each outcome.

Consumer involvement

Due to limited resources, we did not involve consumers in this review. However, as previously described, we will use the COMET core outcome sets for preeclampsia, which were developed with active consumer involvement [82].

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016133.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Cochrane Central Editorial Service supported the authors in the development of this protocol: intervention review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Philippa Middleton, South Australian Health and Medical Research Institute and University of Adelaide;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Leanne V Jones, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Jessenia Hernandez, Cochrane Central Editorial Service;
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- Peer reviewers (provided comments and recommended an editorial decision): Prof A T Lely, UMC Utrecht, WKZ, Department of Obstetrics and Gynaecology (clinical/content review); Anum Minhas, MD MHS, Johns Hopkins University (clinical/content review); Dr Denny Mathew John, Assistant Professor Department of Community Medicine Saveetha Medical College and Hospital, Chennai, India (consumer review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review). One additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

Contributions of authors

GG, TP, MP, AS, TNS, and CSS designed and drafted the protocol. CSS is the guarantor of the review.

Declarations of interest

TP: has no commercial or non-commercial conflicts of interest relevant to this review.

GG: has no commercial or non-commercial conflicts of interest relevant to this review.

MP: received grants from the World Health Organization unrelated to the current review. The author has no commercial or non-commercial conflicts of interest relevant to this review.

TNS: has no commercial or non-commercial conflicts of interest relevant to this review.

AS: the author runs a private practice and is Honorary Secretary of the International Society of Ultrasound in Obstetrics and Gynecology. He is also the president of the Hellenic Society of Ultrasound in Obstetrics and Gynecology. The author has no commercial or non-commercial conflicts of interest relevant to this review.

CSS: the author is an Editor of the Cochrane Gynaecology and Fertility Group but was not involved in the editorial process for this protocol. He also runs a private practice as a Gynecologist after relevant permission from the National and Kapodistrian University of Athens. The author has no commercial or non-commercial conflicts of interest relevant to this review.

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Registration and protocol

Cochrane approved the proposal for this review in February 2024.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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