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Effectiveness of metformin to PCOS pregnant women to reduce abortion and gestational diabetes mellitus: a protocol of an overview of reviews.

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ABSTRACT:

Introduction: Polycystic ovary syndrome (PCOS) is an endocrinological disorder prevalent worldwide. It has been related to poor pregnancy outcomes, such as a higher rate of gestational diabetes and miscarriage. Metformin is one of the drugs studied to improve the prognosis of pregnant women with PCOS**.**

Objective: To carry out an overview of systematic reviews (SR) that studied the effects of metformin versus placebo or no intervention used by pregnant women with the pre-conception diagnosis of polycystic ovary syndrome (PCOS) throughout the pregnancy to reduce the incidence of miscarriage and gestational diabetes.

Methods and analysis: We will carry out an overview of systematic reviews. We will search in Embase; PubMed; Virtual Health Library (LILACS); Cochrane Central Register of Controlled Trials; Trip Database; Scopus; Web of Science; and CINAHL. Language, publication status, and year-indexed or published filters will not be applied. Two reviewers will independently complete screening and select the papers, quality assessment, risk of bias evaluation, and data collection. We will combine the included reviews in a narrative summary. We will prepare a narrative summary with the included SRs. The included studies' quality and risk of bias using AMSTAR2 and ROBIS, respectively.

Ethics and dissemination: This overview of reviews will evaluate data from SR of using metformin for pre-pregnancy diagnosis of PCOS to reduce adverse outcomes. There will be no primary data gathering; hence a formal ethical analysis is unnecessary. We will submit the outcomes of this study in a peer-reviewed journal and at conferences.

Systematic review registration: PROSPERO CRD42023441488

Keywords: Polycystic ovary syndrome; pregnancy; abortion; miscarriage; gestational diabetes; metformin, overview of systematic reviews, study protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- The overview of reviews study can lead to a more robust understanding of the research topic and enhance confidence in the overall conclusions.
- Overviews of reviews provide policymakers, healthcare professionals, and stakeholders with concise, evidence-based summaries. These summaries help inform decision-making processes, guiding the development of guidelines, interventions, and healthcare policies.
- An overview of reviews can highlight areas with limited or conflicting evidence, encouraging investigators to address specific unanswered questions.
- The quality of the overview of reviews heavily relies on the quality of the individual systematic reviews included.
- If the primary reviews have methodological flaws or biases, it can impact the reliability and validity of the overview's conclusions.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by clinical or biochemical evidence of hyperandrogenism, oligo-anovulation, or ultrasonographic diagnosis of a polycystic ovary. The diagnosis of PCOS is made when at least two of these criteria are met according to the Rotterdam diagnostic criteria and recommendations proposed by an international consensus group. [1] The prevalence of PCOS is reported to be between 4% and 18%. [2–6]

The prevalence of obesity in PCOS women can range from 30 to 50%, and they are related in a cyclical manner, where both exacerbate each other. [7] Metabolic syndrome, which is characterized by insulin resistance, dyslipidemia, and hypertension, is frequently associated with PCOS, and the prevalence of metabolic syndrome in women with PCOS range between 1,6% to 43% [8–10] and it is more common when obesity is present.

The condition is highly associated with difficulty conceiving, fertilization treatments, and higher rates of gestational complications, such as miscarriages and gestational diabetes mellitus (GDM). Even though the literature is still controversial about the relationship between adverse pregnancy outcomes and PCOS, miscarriage and GDM are a burden in this group when compared to the general pregnant women. Bahri Khomami et al. conducted a meta-analysis including twenty-one studies that showed a rate of miscarriage up to nearly 60% higher in some groups of PCOS women. [11] Yu et al. (2016) confirmed that PCOS in pregnancy was associated with an increased risk of miscarriage (RR: 2.87; 95% CI: 1.65–4.98) and GDM (RR: 2.78; 95% CI: 2.27–3.40). [12] Regarding GDM, the literature is consistent and points to a greater risk of women with PCOS developing it. [13–16]

Possible treatments for PCOS to reduce adverse outcomes in pregnancy have been studied. Metformin, a biguanide commonly used in type II diabetes mellitus treatment, is one of the most researched medications. [17] A sequence of events could be associated with decreased blood insulin levels: (i) could reduce the concentration of plasminogen activator inhibitor-1; [18,19] (ii) improve uterine vascularization; [20,21] (iii) decrease androgen and LH concentrations; [22,23] (iv) and weight loss in some cases. [20] In theory, these changes would be capable of decreasing the rates of abortion and gestational diabetes.

While we began to register in PROSPERO a new SR about the use of metformin in pregnancy to reduce the incidence of miscarriage and GDM, we identified some published SRs on this subject with discrepant results about it, such as the last two SRs published in 2022. [24,25] We observed possible biases and compromised quality in these reviews.

Thus, we decided to carry out an overview of these systematic reviews, assessing the methodological quality and the risk of bias of the included SRs. This review intends to critically analyze the existing studies on the subject, allowing us to understand whether the information produced so far can support the use of metformin during pregnancy or whether a new higher quality-level systematic review is still necessary.

So, we aim to carry out an overview of SRs that studied the effects of metformin versus placebo, or no intervention, used by pregnant women with the pre-conception diagnosis of PCOS throughout the pregnancy to reduce the incidence of miscarriage and gestational diabetes.

OBJECTIVE

To carry out an overview of SRs that studied the effects of metformin versus placebo or no intervention used by pregnant women with the pre-conception diagnosis of PCOS throughout the pregnancy to reduce the incidence of miscarriage and gestational diabetes.

METHOD

The current study adheres to the guidelines for SRs according to the Cochrane Handbook. (26) To synthesize the available evidence, we will conduct an overview of systematic review following established methods according to the Cochrane Handbook [26] and Preferred Reporting Items for Overviews of Reviews statement (PRIOR). [27] We will evaluate the SRs according to their quality and risk of bias, using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) [28] and ROBIS (Risk Of Bias In Systematic Reviews) checklist. [29] We also will collate the SR results for prespecified outcomes (miscarriage and GDM) and grade the quality of available evidence using the GRADE (Grading of Recommendations Assessment, Development, favoring and Evaluation). [30] The study protocol of this systematic overview was registered in the PROSPERO platform (CRD42023441488).

Eligibility CriteriaWe will add SRs, with or without meta-analyses, which included randomized clinical trials (RCTs) and/or observational studies (non-randomized controlled studies: cohorts), according to the items of the PICOS strategy.

Elements of the PICOS strategy for the research question:

- Population: pregnant women with a pre-conception diagnosis of PCOS.
- Intervention: Using metformin before the pregnancy or starting it in the first trimester.
- Comparison: placebo or no intervention.
- Outcome: incidence of miscarriage and GDM.
- Study type: systematic reviews.

Exclusion criteria

For this study, we will exclude reviews of case reports and of case series, qualitative reviews or reviews that are described as research protocols, experimental studies with animals, studies whose population are women who have undergone ovulation induction with any type of medication or medication and only abstracts (no full texts available). Supplemental primary studies will not be included.

Search Strategy

We will search in Embase [Elsevier] (1980-actual); PubMed [MEDLINE] (1966-2022); Virtual Health Library (LILACS, 1982-2022); Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane); Trip Database; Scopus; Web of Science; and CINAHL. We will use the following MESH words: Polycystic Ovary Syndrome AND Metformin AND (Gestational Diabetes (Diabetes, Gestational) OR Spontaneous Abortion (Abortion, Spontaneous)) AND (Systematic Review OR Meta-analysis). Language, publication

status, and year-indexed or published filters will not be applied. The search strategy is available in Supplement 1. We will export the search results to EndNote X9 (Clarivate Analytics) to remove the duplicate studies before the screening.

Study Selection

After removing the duplicated studies, two independent reviewers will screen all titles and abstracts. Reviewers will review the full-text studies of those potentially eligible. Possible divergences will be solved by consensus or by a third reviewer to ensure the quality of the processes. We will use the Rayyan application, developed by the Qatar Computing Research Institute (QCRI), as an auxiliary tool for archiving, organizing, and selecting the studies.

Data extraction

Reviewers will extract data from the included studies independently way and in pairs. The discrepancy in this stage will be resolved by discussion and consensus.

A standard data extraction form will be used to assess the following information: general characteristics of the studies (author, year of publication, journal name), study type (randomized, non-randomized controlled, non-randomized and non-controlled), number of patients included in each group (Metformin or Placebo/No Medication), the period when metformin or placebo/No Medication was started (before pregnancy or in the first 20 weeks), presence of other associated clinical diseases, the incidence of miscarriage in the first 20 weeks, the incidence of GDM diagnosed between 24 and 28 weeks of gestation.

The data will be grouped in a table to allow the specification of these items. An information grouping will facilitate the comparative analysis of the studies, favoring the identification of the variability among them.

Systematic review - Risk of bias

For each systematic review selected for the study, the ROBIS tool [29] will be applied, which consists of three assessment phases (i. Assessment of relevance; ii. Identification of potential risks of bias during the review process, and iii. Assessment of the overall risk of bias), with phase *ii* consisting of four domains (a. Studies eligibility criteria; b. Studies identification and selection; c. Data collection and studies evaluation; and d. Synthesis and results). The results of the risk of bias appraisal are "high," "low," or "uncertain." Since we assess the risk of bias of the included SRs instead of the consistency between the problem to be solved and the real problem, we only use the second and third stages of ROBIS, considering that the first stage is optional. [16] Similarly, we will adopt the method of independent evaluation by two evaluators. If the evaluation results of the two evaluators are inconsistent, the third evaluator will arbitrate.

Systematic Review - Quality

We will use the AMSTAR 2 tool to assess the methodological quality of the included SRs. It contains 16 questions that address methodology aspects which will be registered with either "yes", "partly yes", or "no", and the results of the final appraisement of the quality of the methodology with either "high", "moderate", "low" or "very low". [28] Two independent reviewers will assess the quality of the methodology in the

included studies using the AMSTAR-2 tool, and in case of disagreement, it will be solved by discussion and consensus.

Assessing the level of evidence (GRADE)

Two independent reviewers will grade of evidence presented by every systematic review for each outcome of interest. We will adhere to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations and assess the following key domains: risk of bias, inconsistency, indirectness, imprecision, and publication/reporting bias. (30) We will resolve the discrepancies through discussion. GRADEpro software will be used to calculate the overall quality of evidence. [31]

Summary of the information

We will combine the included reviews in a narrative summary. The included studies will be presented through a synthesis with information from data extraction described before.

The results will be presented descriptively on the quality and risk of bias of the included systematic review and meta-analysis studies, according to the results by the AMSTAR2 [28] and ROBIS [29] tools used, respectively.

We will report the GRADE [30] for each predefined outcome and subgroup analysis based on the period when metformin or placebo/no medication was started and the metformin dose when it's possible.

REPORTING

The results of this overview will be in accordance with the preferred reporting items for overviews of reviews (PRIOR) statement. [27] We will also use the GRADE Summary of Findings (SoF) tables to summarize the evidence. [30]

DATASET STATEMENT

Research data pertaining to this research will be accessible through the 'Repositório Institucional UNESP' (https://repositorio.unesp.br/). This repository serves as a valuable resource for the academic community and beyond, providing a comprehensive collection of data, findings, and supplementary materials.

DISCUSSION

This overview of reviews about the use of metformin to reduce the incidence of miscarriage and DGM involves systematically identifying, appraising, and synthesizing multiple systematic reviews or meta-analyses. Examining multiple reviews, we can identify a broader range of studies, making it clearer what evidence we have on this. It will provide knowledge about the quality and risk of bias of the reviews, better understanding, and clinically relevant information for clinicians and health decision-makers.

Different reviews may present conflicting findings or reach different conclusions. Analyzing multiple reviews allows us to identify consistent findings across multiple reviews and strengthen the evidence base, while discrepancies may highlight areas of uncertainty or the gap in knowledge about this issue and the need for further research. Additional analyses, such as meta-regression or sensitivity analyses, can be

performed to explore the factors contributing to the discrepancies if it is feasible. Possible inconsistencies can be difficult to draw definitive conclusions or make clear recommendations. Draw definitive conclusions or make clear recommendations.

The evaluation of individual SRs will involve the use of AMSTAR2 [28] and ROBIS [29], which can help health decision-makers to identify high-quality systematic reviews, including those based on observational studies of the use of metformin in pregnant women with PCOS. Understanding the importance of the supporting data might help us better understand the reliability of the inferences made from the reviews. However, there may be variations in the quality of the included reviews, and lower quality SRs can be considered in the analysis but should be interpreted with caution and their limitations acknowledged.

It can take a while to complete an overview of reviews, and there might be a delay until additional research or reviews are published after the overview is finished. The most recent data might not be included in the overview, and after it is finished, new information might become available. To keep the overview current, it should be planned to conduct regular updates or thorough evaluations.

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AUTHOR STATEMENT

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Conflicts of interests

The authors declare that they have no conflict of interest.

Author Contributions

DSN, BLJ, BAS, and JFA were involved in the conception of the study question. DSN, BLJ, BAS, and JFA designed the study methods, inclusion and exclusion criteria, and analysis plans. BLJ and DSF are leading the design of the database search strategies. DSN, BLJ, BAS, and JFA wrote the first draft of the manuscript. LT reviewed the method and the manuscript. All authors contributed to the paper, agreed with its contents, and consented to the publication of the article.

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SUPPLEMENT 1

Search Strategy – 2023, May 31st

Cochrane Central Register of Controlled Trials (CENTRAL)

n = 538

((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary) AND (Metformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin) Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin AND (Abortion, Spontaneous Abortions, Spontaneous OR Spontaneous Abortions OR Spontaneous Abortion OR Early Pregnancy Loss OR Early Pregnancy Losses OR Loss, Early Pregnancy OR Losses, Early Pregnancy OR Pregnancy Loss, Early OR Pregnancy Losses, Early OR Miscarriage OR Miscarriages OR Abortion, Tubal OR Abortions, Tubal OR Tubal Abortion OR Tubal Abortions)) or ((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary ANDMetformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin ANDDiabetes, Gestational OR Diabetes, Pregnancy-Induced OR Diabetes, Pregnancy Induced OR Pregnancy-Induced Diabetes OR Gestational Diabetes OR Diabetes Mellitus, Gestational OR Gestational Diabetes Mellitus))

PubMed [MEDLINE] (1966-2022)

n = 36

(((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Abortion, Spontaneous[Mesh] (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh])) OR ((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Diabetes, Gestational[Mesh] OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh]))

Embase [Elsevier] (1980-2022)

n = 73

(('polycystic ovary syndrome'/exp OR 'polycystic ovary syndrome' OR 'ovary syndrome, polycystic' OR 'syndrome, polycystic ovary' OR 'stein-leventhal syndrome'/exp OR 'stein-leventhal syndrome' OR 'stein

leventhal syndrome'/exp OR 'stein leventhal syndrome' OR 'syndrome, stein-leventhal'/exp OR 'syndrome, stein-leventhal' OR 'sclerocystic ovarian degeneration' OR 'ovarian degeneration, sclerocystic' OR 'sclerocystic ovary syndrome' OR 'polycystic ovarian syndrome' OR 'ovarian syndrome, polycystic' OR 'polycystic ovary syndrome 1' OR 'sclerocystic ovaries' OR 'ovary, sclerocystic' OR 'sclerocystic ovary'/exp OR 'sclerocystic ovary') AND (('metformin'/exp OR metformin) AND dimethylbiguanidine OR dimethylguanylguanidine OR 'glucophage'/exp OR glucophage OR 'metformin hydrochloride'/exp OR 'metformin hydrochloride' OR 'hydrochloride, metformin' OR 'metformin hcl' OR 'hcl, metformin') AND (('abortion, spontaneous'/exp OR 'abortion, spontaneous') AND 'abortions, spontaneous' OR 'spontaneous abortions' OR 'spontaneous abortion'/exp OR 'spontaneous abortion' OR 'early pregnancy loss'/exp OR 'early pregnancy loss' OR 'early pregnancy losses' OR 'loss, early pregnancy' OR 'losses, early pregnancy' OR 'pregnancy loss, early' OR 'pregnancy losses, early' OR 'miscarriage'/exp OR miscarriage OR miscarriages OR 'abortion, tubal' OR 'abortions, tubal' OR 'tubal abortion' OR 'tubal abortions')) AND 'systematic review'/exp

SCOPUS

n = 38

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS("Metformin") ("Dimethylbiguanidine") OR ("Dimethylguanylguanidine") OR ("Glucophage") OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Abortion, Spontaneous") ("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions")) AND ("systematic review")

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS(Metformin) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Diabetes, Gestational") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus")) AND ("systematic review")

Trip Database

n = 1

polycystic ovary syndrome, metformin, abortion or miscarriage

polycystic ovary syndrome, metformin, gestational diabetes

CINAHL

n = 6

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Abortion, Spontaneous+")

("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions"))) AND (systematic review or meta-analysis)

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Diabetes, Gestational+") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus"))) AND (systematic review or meta-analysis)

Web of Science

n = 62

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (glucopage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Abortion, Spontaneous) OR (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions)) and (systematic review)

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Diabetes, Gestational) OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)) and (systematic review) (Todos os campos)

Virtual Health Library (LILACS, 1982-2022)

n = 31

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Diabetes Gestacional) OR (Diabetes, Gestational) OR (Diabète gestationnel) OR (Diabetes Induzida pela Gravidez) OR (Diabetes Induzida por Gravidez) OR (Diabetes Mellitus Gestacional))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Aborto) OR (Abortamento) OR (Abortion) OR (Avortement) OR (Miscarriage))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

Epistemonikos

n = 109

(title:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))) OR abstract:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))))

Effectiveness of metformin to PCOS pregnant women to reduce abortion and gestational diabetes mellitus: a protocol of an overview of reviews - Nassif, DS et al.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 / 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey	5-6

		literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078217.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2023
Complete List of Authors:	Nassif, Darmaris; UNESP, Botucau Medical School - Department of Obstetrics and Gynecology Januário, Bianca; UNESP, Botucau Medical School Sousa, Bianca; UNESP, Botucau Medical School Thabane, Lehana; McMaster University, Department of Health Research Methods, Evidence, and Impact; St Joseph's Healthcare Hamilton, Biostatistics Unit Abbade, Joelcio; UNESP, Botucau Medical School - Department of Obstetrics and Gynaecology; Hospital das Clínicas da Faculdade de Medicina de Botucatu, Maternal Fetal Medicine Unit
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Maternal medicine < OBSTETRICS, Reproductive medicine < GYNAECOLOGY, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews.

Authors
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Word count: 2184 words

ABSTRACT:

Introduction: Polycystic ovary syndrome (PCOS) is a globally prevalent endocrinological disorder. It has been associated with poor pregnancy outcomes, including a higher rate of gestational diabetes and miscarriage. Metformin is among the drugs investigated to improve the prognosis of pregnant women with PCOS**.**

Objective: To conduct an overview of systematic reviews (SR) examining the effects of metformin versus placebo or no intervention throughout pregnancy in pregnant women with a preconception PCOS diagnosis to reduce the incidence of miscarriage and gestational diabetes.

Methods and analysis: We will perform an overview of systematic reviews searching in Embase; PubMed; Virtual Health Library (VHL); Cochrane Central Register of Controlled Trials; Trip Database; Scopus; Web of Science; and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from inception to August 17th, 2023. Language, publication status, and year-indexed or published filters will not be applied. Two reviewers will independently screen and select papers, assess quality, evaluate the risk of bias, and collect data. The included reviews will be summarized narratively. The quality and risk of bias of the systematic review and meta-analysis studies included will be assessed using A Measurement Tool to Assess Systematic Reviews, 2nd version, (AMSTAR-2) and Risk of Bias in Systematic Reviews (ROBIS), respectively.

Ethics and dissemination: This overview of reviews will analyze data from SRs on the use of metformin for pre-pregnancy diagnosis of PCOS to reduce adverse outcomes. As there will be no primary data collection, a formal ethical analysis is unnecessary. The study outcomes will be submitted to a peer-reviewed journal and presented at conferences.

Systematic review registration: PROSPERO CRD42023441488

Keywords: Polycystic ovary syndrome; pregnancy; abortion; miscarriage; gestational diabetes; metformin, overview of systematic reviews, study protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- The overview of reviews study can synthesize evidence from multiple systematic reviews, providing a comprehensive overview of the effectiveness of a particular topic.
- It allows for the identification of consistent findings across multiple reviews as well as contradictions or variations, contributing to a more nuanced understanding of the evidence.
- Systematic reviews included in an overview of reviews may exhibit heterogeneity in terms of methodologies, outcome measures, diagnostic criteria, and participant characteristics, which can pose challenges for synthesis.
- The potential for bias in the original systematic reviews, such as selection bias or interpretation bias, may carry over into the overview of reviews, affecting the validity of the overall findings.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by clinical or biochemical evidence of hyperandrogenism, oligo-anovulation, or ultrasonographic diagnosis of a polycystic ovary. The diagnosis of PCOS is established when at least two of these criteria are met, according to the Rotterdam diagnostic criteria and recommendations proposed by an international consensus group. [1] The prevalence of PCOS is reported to range between 4% and 18%. [2–6]

The prevalence of obesity in PCOS women can vary from 30 to 50%, with a cyclic relationship between these conditions where each exacerbates the other. [7] Metabolic syndrome, characterized by insulin resistance, dyslipidemia, and hypertension, is frequently associated with PCOS, with a prevalence of 1.6% to 43% in women with PCOS [8–10], more commonly when obesity is present.

PCOS is highly associated with difficulties conceiving, fertility treatments, and higher rates of gestational complications, such as miscarriages and gestational diabetes mellitus (GDM). Despite some controversy in the literature regarding the relationship between adverse pregnancy outcomes and PCOS, miscarriage and GDM present a significant burden in this group compared to the general pregnant population. Bahri Khomami et al., in a meta-analysis including twenty-one studies, reported a nearly 60% higher rate of miscarriage in certain groups of women with PCOS. [11] Yu et al. (2016) confirmed that PCOS during pregnancy was associated with an increased risk of miscarriage (RR: 2.87; 95% CI: 1.65–4.98) and GDM (RR: 2.78; 95% CI: 2.27–3.40). [12] Regarding GDM, the literature consistently points to a higher risk for women with PCOS. [13–16]

Various potential treatments for PCOS aimed at reducing adverse pregnancy outcomes have been studied. Metformin, a biguanide commonly used in the treatment of type II diabetes mellitus, is among the most researched medications. [17] The reduction in blood insulin levels attributed to metformin use is believed to have several positive effects, such as: (i) reduction in the concentration of plasminogen activator inhibitor-1; [18,19] (ii) improved uterine vascularization; [20,21] (iii) decreased androgen and LH concentrations; [22,23] (iv) and weight loss in some cases. [20] Theoretically, these changes might decrease rates of abortion and gestational diabetes.

This study was initially planned to be a systematic review on the use of metformin in pregnancy to reduce the incidence of miscarriage and GDM. However, upon attempting to register it in the International Prospective Register of Systematic Reviews (PROSPERO), we discovered published SRs on this subject with discrepant results, such as the last two SRs published in 2022. [24,25] We observed possible biases and compromised quality in these reviews.

Therefore, a decision was made to conduct an overview of these systematic reviews, assessing the methodological quality and the risk of bias of the included SRs. This review aims to critically analyze existing studies on the subject, providing insight into whether the information produced so far supports the use of metformin during pregnancy or whether a new higher quality-level systematic review is still necessary.

Hence, our objective is to perform an overview of SRs studying the effects of metformin versus placebo, or no intervention throughout pregnancy in pregnant women with a preconception diagnosis of PCOS to reduce the incidence of miscarriage and gestational diabetes.

OBJECTIVE

To conduct an overview of SRs examining the effects of metformin versus placebo or no intervention throughout the pregnancy in pregnant women with a preconception PCOS diagnosis to reduce the incidence of miscarriage and gestational diabetes.

METHOD

The present study follows the Cochrane Handbook guidelines for SRs in. (26) To synthesize the available evidence, we will conduct an overview of systematic reviews using established methods outlined in the Cochrane Handbook [26] and the Preferred Reporting Items for Overviews of Reviews statement (PRIOR). [27] The evaluation of SRs will include an assessment of their quality and risk of bias, employing the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) [28] and ROBIS (Risk Of Bias In Systematic Reviews) checklist. [29] Additionally, we will collate the SR results for prespecified outcomes (miscarriage and GDM) and assess the quality of available evidence using the GRADE (Grading of Recommendations Assessment, Development, favoring and Evaluation). [30] The study protocol of this systematic overview was registered on the PROSPERO platform (CRD42023441488). Initiated promptly upon its publication on PROSPERO (July 12, 2023), we aim to complete this overview within a year.

Eligibility Criteria

This overview will include SRs, with or without meta-analyses, which encompass randomized clinical trials (RCTs) and/or observational studies (non-randomized controlled studies: cohorts). Inclusion will be determined based on the criteria outlined in the PICOS (P: population; I: intervention; C: Comparison; O: outcome; S: study type) strategy.

Elements of the PICOS strategy for the research question:

- Population: pregnant women with a preconception diagnosis of PCOS.
- Intervention: Use of metformin before pregnancy or initiation in the first trimester.
- Comparison: placebo or no intervention.
- Outcome: incidence of miscarriage and GDM.
- Study type: systematic reviews.

Exclusion criteria

Reviews of case reports and case series, qualitative reviews or reviews described as research protocols will be excluded, as well as experimental studies involving animals, studies focusing on populations of women who have undergone ovulation induction with any type of medication, and studies with only abstracts available (no full text). Supplemental primary studies will not be included.

Search Strategy

The following databases will be searched: Embase [Elsevier] (1980-actual); PubMed [MEDLINE] (1966-2023); Virtual Health Library (VHL, 1982-2023); Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane); Trip Database; Scopus; Web of Science; and CINAHL. The search will use the following MESH terms: Polycystic Ovary Syndrome AND Metformin AND ((Gestational Diabetes (Diabetes, Gestational) OR Spontaneous Abortion (Abortion, Spontaneous)) AND (Systematic Review OR Meta-analysis). Supplementary methods, such as hand-searching and reference chaining, will be employed in addition to the initial database searches. Language, publication status, and year-indexed or published filters will not be applied. The search strategy is available in Supplement 1. We will include articles published up to August 17th, 2023. The search results will be exported to EndNote™ X9 (Clarivate Analytics) to remove duplicate studies before screening.

Study Selection

Following the elimination of duplicate studies, two independent reviewers will screen all titles and abstracts. The full text of potentially eligible studies will be independently assessed by the reviewers. Any discrepancies will be resolved through consensus to ensure the quality of the processes. The Rayyan application, developed by the Qatar Computing Research Institute (QCRI), will be used as an auxiliary tool for archiving, organizing, and selecting the studies.

Data extraction

Data was extracted by the reviewers independently in pairs. Any discrepancies at this stage will be addressed through discussion and consensus.

A standardized data extraction form will be used to assess the following information: general characteristics of the studies (author, year of publication, journal name), study type (randomized, non-randomized controlled, non-randomized and non-controlled), PCOS diagnostic criteria, number of patients included in each group (Metformin or Placebo/No Medication), the period when metformin or placebo/No Medication was started (before pregnancy or in the first 20 weeks), presence of other associated clinical diseases, the incidence of miscarriage in the first 20 weeks, the incidence of GDM diagnosed between 24 and 28 weeks of gestation.

The data will be organized into a table to facilitate the specification of these items. Grouping the information will enhance the comparative analysis of the studies, aiding in the identification of the variability among them.

Systematic review - Risk of bias

For each systematic review included in the study, the ROBIS tool [29] will be applied encompassing three assessment phases (i. Assessment of relevance; ii. Identification of potential risks of bias during the review process, and iii. Assessment of the overall risk of bias). Phase *ii* consists of four domains (a. Studies eligibility criteria; b. Studies identification and selection; c. Data collection and studies evaluation; and d. Synthesis and results). The results of the risk of bias assessment are categorized as "high," "low," or

"uncertain." Since we will focus on evaluating the risk of bias of the included SRs rather than the consistency between the problem to be solved and the actual problem, only the second and third stages of ROBIS, will be employed, considering the first stage as optional. [16] Similarly, we will adopt the method of independent evaluation by two assessors. In case of inconsistent evaluations between the two assessors, resolution will be achieved through discussion and consensus.

Systematic Review - Quality

The AMSTAR 2 tool will be used to assess the methodological quality of the included SRs. Comprising 16 questions that address various aspects of methodology, responses will be recorded as "yes", "partly yes", or "no", The final appraisal of the methodological quality will be categorized as "high", "moderate", "low" or "very low", based on the responses [28] Two independent reviewers will assess the quality of the methodology in the included studies using the AMSTAR 2 tool, In the event of disagreement, resolution will be achieved through discussion and consensus.

Assessing the level of evidence (GRADE)

Two independent reviewers will grade of evidence presented by each systematic review for every outcome of interest. We will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations assessing the following key domains: risk of bias, inconsistency, indirectness, imprecision, and publication/reporting bias. (30) Discrepancies will be resolved through discussion. The GRADEpro software will be used to calculate the overall quality of evidence. [31]

Summary of the information

The included reviews will be combined in a narrative summary, . presenting the studies through a synthesis with information derived from data extracted as previously described.

The results on the quality and risk of bias of the included studies (as assessed by the AMSTAR 2 [28] and ROBIS [29] tools, respectively),will be presented descriptively .

The GRADE analysis [30] for each predefined outcome and subgroup will be reported based on the period when metformin or placebo/no medication was started and the metformin dose when applicable.

ETHICS AND DISSEMINATION

This research will exclusively use public domain data that does not disclose the identity of research participants, with no involvement of human beings. Therefore, approval from a research ethics committee and consent from research participants for publication are deemed unnecessary.

The results of this overview will align with the preferred reporting items for overviews of reviews (PRIOR) statement. [27] Additionally, the GRADE Summary of Findings (SoF) tables will be employed to

summarize the evidence. [30] The research findings will be published in a peer-reviewed journal, ensuring a rigorous evaluation. Furthermore, we intend to present the findings at academic conferences.

Reporting patient and public involvement in research

It is important to note that there was no involvement of patients or the public in developing the research question and the study's design during the preparation of this study protocol.

Dataset Statement

Research data associated with this study will be be made available through the 'Repositório Institucional UNESP' (https://repositorio.unesp.br/). This repository serves as a valuable resource for the academic community and beyond, offering a comprehensive collection of data, findings, and supplementary materials.

DISCUSSION

This overview of reviews on the use of metformin to reduce the incidence of miscarriage and GDM will take a systematically approach involving the identification, appraisal, and synthesis of multiple systematic reviews or meta-analyses. By examining multiple reviews, we will be able to identify a broader range of studies, enhancing the clarity of available evidence on this topic. Thus, it will contribute valuable insights into the quality and risk of bias associated with the reviews, offering better clinicians and health decision-makers clinically relevant information.

Diversity in findings leading to conflicting conclusions across different reviews is anticipated. However, this diversity will allow us to identify consistent findings, strengthening the evidence base. Discrepancies may highlight areas of uncertainty or gaps in knowledge, signaling the need for further research. Additional analyses, such as meta-regression or sensitivity analyses, may be performed, if feasible, to explore the factors contributing to discrepancies. Despite efforts to draw definitive conclusions or provide clear recommendations, possible inconsistencies may pose challenges.

Evaluating each SR using the AMSTAR2 [28] and ROBIS [29], will enable health decision-makers to discern high-quality systematic reviews, even those based on observational studies of metformin use in pregnant women with PCOS. Recognizing the importance of the supporting data might enhance our understanding of the reliability of inferences derived from the reviews. However, considering potential variations in the quality of the included reviews is crucial Lower quality SRs, if included in the analysis, should be interpreted with caution and their limitations duly noted.

The duration required for completing an overview of reviews and potential delays until additional research or reviews are published post-completion are acknowledged challenges. To ensure the ongoing relevance of the overview, regular updates or thorough evaluations should be planned to incorporate the most recent data and insights.

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AUTHOR STATEMENT

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Conflicts of interests

The authors declare that they have no conflict of interest.

Author Contributions

DSN, BLJ, BAS, and JFA were involved in the conception of the study question. DSN, BLJ, BAS, and JFA designed the study methods, inclusion and exclusion criteria, and analysis plans. BLJ and DSF are leading the design of the database search strategies. DSN, BLJ, BAS, and JFA wrote the first draft of the manuscript. LT reviewed the method and the manuscript. All authors contributed to the paper, agreed with its contents, and consented to the publication of the article.

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SUPPLEMENT 1

Search Strategy – 2023, August 17st

Cochrane Central Register of Controlled Trials (CENTRAL)

n = 538

((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary) AND (Metformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin) Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin AND (Abortion, Spontaneous Abortions, Spontaneous OR Spontaneous Abortions OR Spontaneous Abortion OR Early Pregnancy Loss OR Early Pregnancy Losses OR Loss, Early Pregnancy OR Losses, Early Pregnancy OR Pregnancy Loss, Early OR Pregnancy Losses, Early OR Miscarriage OR Miscarriages OR Abortion, Tubal OR Abortions, Tubal OR Tubal Abortion OR Tubal Abortions)) or ((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary ANDMetformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin ANDDiabetes, Gestational OR Diabetes, Pregnancy-Induced OR Diabetes, Pregnancy Induced OR Pregnancy-Induced Diabetes OR Gestational Diabetes OR Diabetes Mellitus, Gestational OR Gestational Diabetes Mellitus))

PubMed [MEDLINE] (1966-2022)

n = 39

(((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Abortion, Spontaneous[Mesh] (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh])) OR ((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Diabetes, Gestational[Mesh] OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh]))

Embase [Elsevier] (1980-2022)

n = 73

(('polycystic ovary syndrome'/exp OR 'polycystic ovary syndrome' OR 'ovary syndrome, polycystic' OR 'syndrome, polycystic ovary' OR 'stein-leventhal syndrome'/exp OR 'stein-leventhal syndrome' OR 'stein

leventhal syndrome'/exp OR 'stein leventhal syndrome' OR 'syndrome, stein-leventhal'/exp OR 'syndrome, stein-leventhal' OR 'sclerocystic ovarian degeneration' OR 'ovarian degeneration, sclerocystic' OR 'sclerocystic ovary syndrome' OR 'polycystic ovarian syndrome' OR 'ovarian syndrome, polycystic' OR 'polycystic ovary syndrome 1' OR 'sclerocystic ovaries' OR 'ovary, sclerocystic' OR 'sclerocystic ovary'/exp OR 'sclerocystic ovary') AND (('metformin'/exp OR metformin) AND dimethylbiguanidine OR dimethylguanylguanidine OR 'glucophage'/exp OR glucophage OR 'metformin hydrochloride'/exp OR 'metformin hydrochloride' OR 'hydrochloride, metformin' OR 'metformin hcl' OR 'hcl, metformin') AND (('abortion, spontaneous'/exp OR 'abortion, spontaneous') AND 'abortions, spontaneous' OR 'spontaneous abortions' OR 'spontaneous abortion'/exp OR 'spontaneous abortion' OR 'early pregnancy loss'/exp OR 'early pregnancy loss' OR 'early pregnancy losses' OR 'loss, early pregnancy' OR 'losses, early pregnancy' OR 'pregnancy loss, early' OR 'pregnancy losses, early' OR 'miscarriage'/exp OR miscarriage OR miscarriages OR 'abortion, tubal' OR 'abortions, tubal' OR 'tubal abortion' OR 'tubal abortions')) AND 'systematic review'/exp

SCOPUS

n = 38

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS("Metformin") ("Dimethylbiguanidine") OR ("Dimethylguanylguanidine") OR ("Glucophage") OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Abortion, Spontaneous") ("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions")) AND ("systematic review")

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS(Metformin) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Diabetes, Gestational") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus")) AND ("systematic review")

Trip Database

n = 1

polycystic ovary syndrome, metformin, abortion or miscarriage

polycystic ovary syndrome, metformin, gestational diabetes

CINAHL

n = 6

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Abortion, Spontaneous+")

("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions"))) AND (systematic review or meta-analysis)

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Diabetes, Gestational+") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus"))) AND (systematic review or meta-analysis)

Web of Science

n = 62

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (glucopage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Abortion, Spontaneous) OR (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions)) and (systematic review)

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Diabetes, Gestational) OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)) and (systematic review) (Todos os campos)

Virtual Health Library (LILACS, 1982-2022)

n = 31

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Diabetes Gestacional) OR (Diabetes, Gestational) OR (Diabète gestationnel) OR (Diabetes Induzida pela Gravidez) OR (Diabetes Induzida por Gravidez) OR (Diabetes Mellitus Gestacional))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Aborto) OR (Abortamento) OR (Abortion) OR (Avortement) OR (Miscarriage))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

Epistemonikos

n = 109

(title:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))) OR abstract:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))))

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews. - Nassif, DS et al.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 / 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey	5-6

		literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews.

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Manuscript ID	bmjopen-2023-078217.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Feb-2024
Complete List of Authors:	Nassif, Darmaris; UNESP, Botucau Medical School - Department of Obstetrics and Gynecology Januário, Bianca; UNESP, Botucau Medical School Sousa, Bianca; UNESP, Botucau Medical School Thabane, Lehana; McMaster University, Department of Health Research Methods, Evidence, and Impact; St Joseph's Healthcare Hamilton, Biostatistics Unit Abbade, Joelcio; Universidade Estadual Paulista Julio de Mesquita Filho Faculdade de Medicina Campus de Botucatu, Obstetric and Gynecology;
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Maternal medicine < OBSTETRICS, Reproductive medicine < GYNAECOLOGY, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews.

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Word count: 2184 words

ABSTRACT:

Introduction: Polycystic ovary syndrome (PCOS) is a globally prevalent endocrinological disorder. It has been associated with poor pregnancy outcomes, including a higher rate of gestational diabetes and miscarriage. Metformin is among the drugs investigated to improve the prognosis of pregnant women with PCOS**.**

Objective: To conduct an overview of systematic reviews (SR) examining the effects of metformin versus placebo or no intervention throughout pregnancy in pregnant women with a preconception PCOS diagnosis to reduce the incidence of miscarriage and gestational diabetes.

Methods and analysis: We will perform an overview of systematic reviews searching in Embase; PubMed; Virtual Health Library (VHL); Cochrane Central Register of Controlled Trials; Trip Database; Scopus; Web of Science; and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from inception to August 17th, 2023. Language, publication status, and year-indexed or published filters will not be applied. Two reviewers will independently screen and select papers, assess quality, evaluate the risk of bias, and collect data. The included reviews will be summarized narratively. The quality and risk of bias of the systematic review and meta-analysis studies included will be assessed using A Measurement Tool to Assess Systematic Reviews, 2nd version, (AMSTAR-2) and Risk of Bias in Systematic Reviews (ROBIS), respectively.

Ethics and dissemination: This overview of reviews will analyze data from SRs on the use of metformin for pre-pregnancy diagnosis of PCOS to reduce adverse outcomes. As there will be no primary data collection, a formal ethical analysis is unnecessary. The study outcomes will be submitted to a peer-reviewed journal and presented at conferences.

Systematic review registration: PROSPERO CRD42023441488

Keywords: Polycystic ovary syndrome; pregnancy; abortion; miscarriage; gestational diabetes; metformin, overview of systematic reviews, study protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- The overview of reviews study can synthesize evidence from multiple systematic reviews, providing a comprehensive overview of the effectiveness of a particular topic.
- It allows for the identification of consistent findings across multiple reviews as well as contradictions or variations, contributing to a more nuanced understanding of the evidence.
- Systematic reviews included in an overview of reviews may exhibit heterogeneity in terms of methodologies, outcome measures, diagnostic criteria, and participant characteristics, which can pose challenges for synthesis.
- The potential for bias in the original systematic reviews, such as selection bias or interpretation bias, may carry over into the overview of reviews, affecting the validity of the overall findings.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by clinical or biochemical evidence of hyperandrogenism, oligo-anovulation, or ultrasonographic diagnosis of a polycystic ovary. The diagnosis of PCOS is established when at least two of these criteria are met, according to the Rotterdam diagnostic criteria and recommendations proposed by an international consensus group. [1] The prevalence of PCOS is reported to range between 4% and 18%. [2–6]

The prevalence of obesity in PCOS women can vary from 30 to 50%, with a cyclic relationship between these conditions where each exacerbates the other. [7] Metabolic syndrome, characterized by insulin resistance, dyslipidemia, and hypertension, is frequently associated with PCOS, with a prevalence of 1.6% to 43% in women with PCOS [8–10], more commonly when obesity is present.

PCOS is highly associated with difficulties conceiving, fertility treatments, and higher rates of gestational complications, such as miscarriages and gestational diabetes mellitus (GDM). Despite some controversy in the literature regarding the relationship between adverse pregnancy outcomes and PCOS, miscarriage and GDM present a significant burden in this group compared to the general pregnant population. Bahri Khomami et al., in a meta-analysis including twenty-one studies, reported a nearly 60% higher rate of miscarriage in certain groups of women with PCOS. [11] Yu et al. (2016) confirmed that PCOS during pregnancy was associated with an increased risk of miscarriage (RR: 2.87; 95% CI: 1.65–4.98) and GDM (RR: 2.78; 95% CI: 2.27–3.40). [12] Regarding GDM, the literature consistently points to a higher risk for women with PCOS. [13–16]

Various potential treatments for PCOS aimed at reducing adverse pregnancy outcomes have been studied. Metformin, a biguanide commonly used in the treatment of type II diabetes mellitus, is among the most researched medications. [17] The reduction in blood insulin levels attributed to metformin use is believed to have several positive effects, such as: (i) reduction in the concentration of plasminogen activator inhibitor-1; [18,19] (ii) improved uterine vascularization; [20,21] (iii) decreased androgen and LH concentrations; [22,23] (iv) and weight loss in some cases. [20] Theoretically, these changes might decrease rates of abortion and gestational diabetes.

This study was initially planned to be a systematic review on the use of metformin in pregnancy to reduce the incidence of miscarriage and GDM. However, upon attempting to register it in the International Prospective Register of Systematic Reviews (PROSPERO), we discovered published SRs on this subject with discrepant results, such as the last two SRs published in 2022. [24,25] We observed possible biases and compromised quality in these reviews.

Therefore, a decision was made to conduct an overview of these systematic reviews, assessing the methodological quality and the risk of bias of the included SRs. This review aims to critically analyze existing studies on the subject, providing insight into whether the information produced so far supports the use of metformin during pregnancy or whether a new higher quality-level systematic review is still necessary.

Hence, our objective is to perform an overview of SRs studying the effects of metformin versus placebo, or no intervention throughout pregnancy in pregnant women with a preconception diagnosis of PCOS to reduce the incidence of miscarriage and gestational diabetes.

OBJECTIVE

To conduct an overview of SRs examining the effects of metformin versus placebo or no intervention throughout the pregnancy in pregnant women with a preconception PCOS diagnosis to reduce the incidence of miscarriage and gestational diabetes.

METHOD

The present study follows the Cochrane Handbook guidelines for SRs in. (26) To synthesize the available evidence, we will conduct an overview of systematic reviews using established methods outlined in the Cochrane Handbook [26] and the Preferred Reporting Items for Overviews of Reviews statement (PRIOR). [27] The evaluation of SRs will include an assessment of their quality and risk of bias, employing the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) [28] and ROBIS (Risk Of Bias In Systematic Reviews) checklist. [29] Additionally, we will collate the SR results for prespecified outcomes (miscarriage and GDM) and assess the quality of available evidence using the GRADE (Grading of Recommendations Assessment, Development, favoring and Evaluation). [30] The study protocol of this systematic overview was registered on the PROSPERO platform (CRD42023441488). Initiated promptly upon its publication on PROSPERO (July 12, 2023), we aim to complete this overview within a year.

Eligibility Criteria

This overview will include SRs, with or without meta-analyses, which encompass randomized clinical trials (RCTs) and/or observational studies (non-randomized controlled studies: cohorts). Inclusion will be determined based on the criteria outlined in the PICOS (P: population; I: intervention; C: Comparison; O: outcome; S: study type) strategy.

Elements of the PICOS strategy for the research question:

- Population: pregnant women with a preconception diagnosis of PCOS.
- Intervention: Use of metformin before pregnancy or initiation in the first trimester.
- Comparison: placebo or no intervention.
- Outcome: incidence of miscarriage and GDM.
- Study type: systematic reviews.

Exclusion criteria

Reviews of case reports and case series, qualitative reviews or reviews described as research protocols will be excluded, as well as experimental studies involving animals, studies focusing on populations of women who have undergone ovulation induction with any type of medication, and studies with only abstracts available (no full text). Supplemental primary studies will not be included.

Search Strategy

The following databases will be searched: Embase [Elsevier] (1980-actual); PubMed [MEDLINE] (1966-2023); Virtual Health Library (VHL, 1982-2023); Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane); Trip Database; Scopus; Web of Science; and CINAHL. The search will use the following MESH terms: Polycystic Ovary Syndrome AND Metformin AND ((Gestational Diabetes (Diabetes, Gestational) OR Spontaneous Abortion (Abortion, Spontaneous)) AND (Systematic Review OR Meta-analysis). Supplementary methods, such as hand-searching and reference chaining, will be employed in addition to the initial database searches. Language, publication status, and year-indexed or published filters will not be applied. The search strategy is available in Supplement 1. We will include articles published up to August 17th, 2023. The search results will be exported to EndNote™ X9 (Clarivate Analytics) to remove duplicate studies before screening.

Study Selection

Following the elimination of duplicate studies, two independent reviewers will screen all titles and abstracts. The full text of potentially eligible studies will be independently assessed by the reviewers. Any discrepancies will be resolved through consensus to ensure the quality of the processes. The Rayyan application, developed by the Qatar Computing Research Institute (QCRI), will be used as an auxiliary tool for archiving, organizing, and selecting the studies.

Data extraction

Data was extracted by the reviewers independently in pairs. Any discrepancies at this stage will be addressed through discussion and consensus.

A standardized data extraction form will be used to assess the following information: general characteristics of the studies (author, year of publication, journal name), study type (randomized, non-randomized controlled, non-randomized and non-controlled), PCOS diagnostic criteria, number of patients included in each group (Metformin or Placebo/No Medication), the period when metformin or placebo/No Medication was started (before pregnancy or in the first 20 weeks), presence of other associated clinical diseases, the incidence of miscarriage in the first 20 weeks, the incidence of GDM diagnosed between 24 and 28 weeks of gestation.

The data will be organized into a table to facilitate the specification of these items. Grouping the information will enhance the comparative analysis of the studies, aiding in the identification of the variability among them.

Systematic review - Risk of bias

For each systematic review included in the study, the ROBIS tool [29] will be applied encompassing three assessment phases (i. Assessment of relevance; ii. Identification of potential risks of bias during the review process, and iii. Assessment of the overall risk of bias). Phase *ii* consists of four domains (a. Studies eligibility criteria; b. Studies identification and selection; c. Data collection and studies evaluation; and d. Synthesis and results). The results of the risk of bias assessment are categorized as "high," "low," or

"uncertain." Since we will focus on evaluating the risk of bias of the included SRs rather than the consistency between the problem to be solved and the actual problem, only the second and third stages of ROBIS, will be employed, considering the first stage as optional. [16] Similarly, we will adopt the method of independent evaluation by two assessors. In case of inconsistent evaluations between the two assessors, resolution will be achieved through discussion and consensus.

Systematic Review - Quality

The AMSTAR 2 tool will be used to assess the methodological quality of the included SRs. Comprising 16 questions that address various aspects of methodology, responses will be recorded as "yes", "partly yes", or "no", The final appraisal of the methodological quality will be categorized as "high", "moderate", "low" or "very low", based on the responses [28] Two independent reviewers will assess the quality of the methodology in the included studies using the AMSTAR 2 tool, In the event of disagreement, resolution will be achieved through discussion and consensus.

Assessing the level of evidence (GRADE)

Two independent reviewers will grade of evidence presented by each systematic review for every outcome of interest. We will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations assessing the following key domains: risk of bias, inconsistency, indirectness, imprecision, and publication/reporting bias. (30) Discrepancies will be resolved through discussion. The GRADEpro software will be used to calculate the overall quality of evidence. [31]

Summary of the information

The included reviews will be combined in a narrative summary, presenting the studies through a synthesis with information derived from data extracted as previously described. Considering that the diagnostic criteria for PCOS may vary, we will perform a subgroup analysis with different PCOS criteria.

The results on the quality and risk of bias of the included studies (as assessed by the AMSTAR 2 [28] and ROBIS [29] tools, respectively) will be presented descriptively.

The GRADE analysis [30] for each predefined outcome and subgroup will be reported based on the period when metformin or placebo/no medication was started and the metformin dose when applicable.

ETHICS AND DISSEMINATION

This research will exclusively use public domain data that does not disclose the identity of research participants, with no involvement of human beings. Therefore, approval from a research ethics committee and consent from research participants for publication are deemed unnecessary.

The results of this overview will align with the preferred reporting items for overviews of reviews (PRIOR) statement. [27] Additionally, the GRADE Summary of Findings (SoF) tables will be employed to

summarize the evidence. [30] The research findings will be published in a peer-reviewed journal, ensuring a rigorous evaluation. Furthermore, we intend to present the findings at academic conferences.

Reporting patient and public involvement in research

It is important to note that there was no involvement of patients or the public in developing the research question and the study's design during the preparation of this study protocol.

Dataset Statement

Research data associated with this study will be be made available through the 'Repositório Institucional UNESP' (https://repositorio.unesp.br/). This repository serves as a valuable resource for the academic community and beyond, offering a comprehensive collection of data, findings, and supplementary materials.

DISCUSSION

This overview of reviews on the use of metformin to reduce the incidence of miscarriage and GDM will take a systematically approach involving the identification, appraisal, and synthesis of multiple systematic reviews or meta-analyses. By examining multiple reviews, we will be able to identify a broader range of studies, enhancing the clarity of available evidence on this topic. Thus, it will contribute valuable insights into the quality and risk of bias associated with the reviews, offering better clinicians and health decision-makers clinically relevant information.

Diversity in findings leading to conflicting conclusions across different reviews is anticipated. However, this diversity will allow us to identify consistent findings, strengthening the evidence base. Discrepancies may highlight areas of uncertainty or gaps in knowledge, signaling the need for further research. Additional analyses, such as meta-regression or sensitivity analyses, may be performed, if feasible, to explore the factors contributing to discrepancies. Despite efforts to draw definitive conclusions or provide clear recommendations, possible inconsistencies may pose challenges.

Evaluating each SR using the AMSTAR2 [28] and ROBIS [29], will enable health decision-makers to discern high-quality systematic reviews, even those based on observational studies of metformin use in pregnant women with PCOS. Recognizing the importance of the supporting data might enhance our understanding of the reliability of inferences derived from the reviews. However, considering potential variations in the quality of the included reviews is crucial Lower quality SRs, if included in the analysis, should be interpreted with caution and their limitations duly noted.

The duration required for completing an overview of reviews and potential delays until additional research or reviews are published post-completion are acknowledged challenges. To ensure the ongoing relevance of the overview, regular updates or thorough evaluations should be planned to incorporate the most recent data and insights.

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AUTHOR STATEMENT

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Conflicts of interests

The authors declare that they have no conflict of interest.

Author Contributions

DSN, BLJ, BAS, and JFA were involved in the conception of the study question. DSN, BLJ, BAS, and JFA designed the study methods, inclusion and exclusion criteria, and analysis plans. BLJ and DSF are leading the design of the database search strategies. DSN, BLJ, BAS, and JFA wrote the first draft of the manuscript. LT reviewed the method and the manuscript. All authors contributed to the paper, agreed with its contents, and consented to the publication of the article.

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SUPPLEMENT 1

Search Strategy – 2023, August 17st

Cochrane Central Register of Controlled Trials (CENTRAL)

n = 538

((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary) AND (Metformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin) Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin AND (Abortion, Spontaneous Abortions, Spontaneous OR Spontaneous Abortions OR Spontaneous Abortion OR Early Pregnancy Loss OR Early Pregnancy Losses OR Loss, Early Pregnancy OR Losses, Early Pregnancy OR Pregnancy Loss, Early OR Pregnancy Losses, Early OR Miscarriage OR Miscarriages OR Abortion, Tubal OR Abortions, Tubal OR Tubal Abortion OR Tubal Abortions)) or ((Polycystic Ovary Syndrome OR Ovary Syndrome, Polycystic OR Syndrome, Polycystic Ovary OR Stein-Leventhal Syndrome OR Stein Leventhal Syndrome OR Syndrome, Stein-Leventhal OR Sclerocystic Ovarian Degeneration OR Ovarian Degeneration, Sclerocystic OR Sclerocystic Ovary Syndrome OR Polycystic Ovarian Syndrome OR Ovarian Syndrome, Polycystic OR Polycystic Ovary Syndrome 1 OR Sclerocystic Ovaries OR Ovary, Sclerocystic OR Sclerocystic Ovary ANDMetformin Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage OR Metformin Hydrochloride OR Hydrochloride, Metformin OR Metformin HCl OR HCl, Metformin ANDDiabetes, Gestational OR Diabetes, Pregnancy-Induced OR Diabetes, Pregnancy Induced OR Pregnancy-Induced Diabetes OR Gestational Diabetes OR Diabetes Mellitus, Gestational OR Gestational Diabetes Mellitus))

PubMed [MEDLINE] (1966-2022)

n = 39

(((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Abortion, Spontaneous[Mesh] (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh])) OR ((((Polycystic Ovary Syndrome[Mesh] OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (Sclerocystic Ovarian Degeneration) OR (Ovarian Degeneration, Sclerocystic) OR (Sclerocystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (Sclerocystic Ovaries) OR (Ovary, Sclerocystic) OR (Sclerocystic Ovary)) AND (Metformin[Mesh] (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin))) AND (Diabetes, Gestational[Mesh] OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)))) AND ((Systematic Review [Publication Type]) OR Systematic Reviews as Topic[Mesh]))

Embase [Elsevier] (1980-2022)

n = 73

(('polycystic ovary syndrome'/exp OR 'polycystic ovary syndrome' OR 'ovary syndrome, polycystic' OR 'syndrome, polycystic ovary' OR 'stein-leventhal syndrome'/exp OR 'stein-leventhal syndrome' OR 'stein

leventhal syndrome'/exp OR 'stein leventhal syndrome' OR 'syndrome, stein-leventhal'/exp OR 'syndrome, stein-leventhal' OR 'sclerocystic ovarian degeneration' OR 'ovarian degeneration, sclerocystic' OR 'sclerocystic ovary syndrome' OR 'polycystic ovarian syndrome' OR 'ovarian syndrome, polycystic' OR 'polycystic ovary syndrome 1' OR 'sclerocystic ovaries' OR 'ovary, sclerocystic' OR 'sclerocystic ovary'/exp OR 'sclerocystic ovary') AND (('metformin'/exp OR metformin) AND dimethylbiguanidine OR dimethylguanylguanidine OR 'glucophage'/exp OR glucophage OR 'metformin hydrochloride'/exp OR 'metformin hydrochloride' OR 'hydrochloride, metformin' OR 'metformin hcl' OR 'hcl, metformin') AND (('abortion, spontaneous'/exp OR 'abortion, spontaneous') AND 'abortions, spontaneous' OR 'spontaneous abortions' OR 'spontaneous abortion'/exp OR 'spontaneous abortion' OR 'early pregnancy loss'/exp OR 'early pregnancy loss' OR 'early pregnancy losses' OR 'loss, early pregnancy' OR 'losses, early pregnancy' OR 'pregnancy loss, early' OR 'pregnancy losses, early' OR 'miscarriage'/exp OR miscarriage OR miscarriages OR 'abortion, tubal' OR 'abortions, tubal' OR 'tubal abortion' OR 'tubal abortions')) AND 'systematic review'/exp

SCOPUS

n = 38

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS("Metformin") ("Dimethylbiguanidine") OR ("Dimethylguanylguanidine") OR ("Glucophage") OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Abortion, Spontaneous") ("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions")) AND ("systematic review")

((INDEXTERMS("Polycystic Ovary Syndrome") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND (INDEXTERMS(Metformin) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND (INDEXTERMS("Diabetes, Gestational") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus")) AND ("systematic review")

Trip Database

n = 1

polycystic ovary syndrome, metformin, abortion or miscarriage

polycystic ovary syndrome, metformin, gestational diabetes

CINAHL

n = 6

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Abortion, Spontaneous+")

("Abortions, Spontaneous") OR ("Spontaneous Abortions") OR ("Spontaneous Abortion") OR ("Early Pregnancy Loss") OR ("Early Pregnancy Losses") OR ("Loss, Early Pregnancy") OR ("Losses, Early Pregnancy") OR ("Pregnancy Loss, Early") OR ("Pregnancy Losses, Early") OR (Miscarriage) OR (Miscarriages) OR ("Abortion, Tubal") OR ("Abortions, Tubal") OR ("Tubal Abortion") OR ("Tubal Abortions"))) AND (systematic review or meta-analysis)

((((MH "Polycystic Ovary Syndrome+") OR ("Ovary Syndrome, Polycystic") OR ("Syndrome, Polycystic Ovary") OR ("Stein-Leventhal Syndrome") OR ("Stein Leventhal Syndrome") OR ("Syndrome, Stein-Leventhal") OR ("Sclerocystic Ovarian Degeneration") OR ("Ovarian Degeneration, Sclerocystic") OR ("Sclerocystic Ovary Syndrome") OR ("Polycystic Ovarian Syndrome") OR ("Ovarian Syndrome, Polycystic") OR ("Polycystic Ovary Syndrome 1") OR ("Sclerocystic Ovaries") OR ("Ovary, Sclerocystic") OR ("Sclerocystic Ovary")) AND ((MH Metformin+) (Dimethylbiguanidine) OR (Dimethylguanylguanidine) OR (Glucophage) OR ("Metformin Hydrochloride") OR ("Hydrochloride, Metformin") OR ("Metformin HCl") OR ("HCl, Metformin"))) AND ((MH "Diabetes, Gestational+") OR ("Diabetes, Pregnancy-Induced") OR ("Diabetes, Pregnancy Induced") OR ("Pregnancy-Induced Diabetes") OR ("Gestational Diabetes") OR ("Diabetes Mellitus, Gestational") OR ("Gestational Diabetes Mellitus"))) AND (systematic review or meta-analysis)

Web of Science

n = 62

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (glucopage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Abortion, Spontaneous) OR (Abortions, Spontaneous) OR (Spontaneous Abortions) OR (Spontaneous Abortion) OR (Early Pregnancy Loss) OR (Early Pregnancy Losses) OR (Loss, Early Pregnancy) OR (Losses, Early Pregnancy) OR (Pregnancy Loss, Early) OR (Pregnancy Losses, Early) OR (Miscarriage) OR (Miscarriages) OR (Abortion, Tubal) OR (Abortions, Tubal) OR (Tubal Abortion) OR (Tubal Abortions)) and (systematic review)

((Polycystic Ovary Syndrome) OR (Ovary Syndrome, Polycystic) OR (Syndrome, Polycystic Ovary) OR (Stein-Leventhal Syndrome) OR (Stein Leventhal Syndrome) OR (Syndrome, Stein-Leventhal) OR (sclerocystis Ovarian Degeneration) OR (Ovarian Degeneration, sclerocystis) OR (sclerocystis Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (Ovarian Syndrome, Polycystic) OR (Polycystic Ovary Syndrome 1) OR (sclerocystis Ovaries) OR (Ovary, sclerocystis) OR (sclerocystis Ovary)) and ((Metformin) or (dimethylbiguanidium) OR (Dimethylguanylguanidine) OR (Glucophage) OR (Metformin Hydrochloride) OR (Hydrochloride, Metformin) OR (Metformin HCl) OR (HCl, Metformin)) and ((Diabetes, Gestational) OR (Diabetes, Pregnancy-Induced) OR (Diabetes, Pregnancy Induced) OR (Pregnancy-Induced Diabetes) OR (Gestational Diabetes) OR (Diabetes Mellitus, Gestational) OR (Gestational Diabetes Mellitus)) and (systematic review) (Todos os campos)

Virtual Health Library (LILACS, 1982-2022)

n = 31

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Diabetes Gestacional) OR (Diabetes, Gestational) OR (Diabète gestationnel) OR (Diabetes Induzida pela Gravidez) OR (Diabetes Induzida por Gravidez) OR (Diabetes Mellitus Gestacional))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

(((Síndrome do Ovário Policístico) or (Polycystic Ovary Syndrome) or (Síndrome del Ovario Poliquístico) or (Syndrome des ovaires polykystiques)) AND (metformina or metformin or metformine or (Dimetil Guanil Guanidina)) and ((Aborto) OR (Abortamento) OR (Abortion) OR (Avortement) OR (Miscarriage))) AND ((Revisão Sistemática) OR (Systematic Review) OR (Revisión Sistemática) OR (Revue systématique))

Epistemonikos

n = 109

(title:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))) OR abstract:((title:(Polycystic Ovary Syndrome) OR abstract:(Polycystic Ovary Syndrome)) AND (title:(Metformin) OR abstract:(Metformin)) AND (title:((abortion OR miscarriage) OR (gestational diabetes mellitus)) OR abstract:((abortion OR miscarriage) OR (gestational diabetes mellitus)))))

Effectiveness of metformin to PCOS pregnant women to reduce spontaneous abortion and gestational diabetes mellitus: a protocol for an overview of reviews. - Nassif, DS et al.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 / 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey	5-6

		literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	-
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.