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

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ABSTRACT

Introduction Polycystic ovary syndrome (PCOS) is a globally prevalent endocrinological disorder and 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 examining the effects of metformin versus placebo or no intervention throughout pregnancy among 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 by searching Embase, PubMed, Virtual Health Library, Cochrane Central Register of Controlled Trials, Trip Database, Scopus, Web of Science and Cumulative Index to Nursing and Allied Health Literature from inception to 17 August 2023. Language, publication status and year indexed or published filters will not be applied. Two reviewers will independently screen and select papers, assess their quality, evaluate their risk of bias and collect the data. The included reviews will be summarised narratively. The quality and risk of bias of the systematic review and meta-analysis studies included will be assessed using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, Second Version) and ROBIS (Risk of Bias in Systematic Reviews), respectively.

Ethics and dissemination This overview of reviews will analyse data from systematic reviews on the use of metformin for prepregnancy 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.

PROSPERO registration number CRD42023441488.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Performing an overview of review studies can synthesise evidence from multiple systematic reviews, providing a comprehensive overview of the effectiveness of a particular topic.
⇒ An overview allows for 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 characterised by clinical or biochemical evidence of hyperandrogenism and oligoanovulation 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 the 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 women with PCOS can vary from 30% to 50%, with a cyclic relationship between these conditions, where each exacerbates the other.[7] Metabolic syndrome, characterised by insulin resistance, dyslipidaemia and hypertension, is frequently associated with PCOS, with a prevalence of 1.6%–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 with the general pregnant population. Bahri Khomami *et al*, in a meta-analysis including 21 studies, reported a nearly 60% higher rate of miscarriage in certain groups of women with PCOS.[11] Yu *et al*[12] confirmed that PCOS during pregnancy was associated with an increased risk of miscarriage (RR (relative risk) : 2.87; 95% CI 1.65 to 4.98) and GDM (RR: 2.78; 95% CI 2.27 to 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 2 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 (1) reduction in the concentration of plasminogen activator inhibitor-1,[18 19] (2) improved uterine vascularisation,[20 21] (3) decreased androgen and LH concentrations[22 23] (4) and weight loss in some cases.[20] Theoretically, these changes might decrease the rates of abortion and gestational diabetes.

This study was initially planned to be a systematic review (SR) on the use of metformin in pregnancy to reduce the incidence of miscarriage and GDM. However, on 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 SRs, assessing the methodological quality and the risk of bias of the included SRs. This review aims to critically analyse 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 SR is necessary.

Objective

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

METHODS

The present study follows the Cochrane Handbook guidelines for SRs used in Pollock *et al*.[26] To synthesise the available evidence, we will conduct an overview of SRs using established methods outlined in the Cochrane Handbook[26] and the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement.[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) online supplemental checklist.[29]

Additionally, we will collate the SR results for prespecified outcomes (miscarriage and GDM) and assess the quality of available evidence using GRADE (Grading of Recommendations Assessment, Development, favouring and Evaluation).[30] The study protocol for this systematic overview was registered on the PROSPERO platform (CRD42023441488). Initiated promptly on its publication on PROSPERO (12 July 2023), we aim to complete this overview within a year.

Eligibility criteria

This overview will include SRs, with or without meta-analyses, which encompass randomised clinical trials and/or observational studies (non-randomised 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.

The following are the elements of the research question following the PICOS strategy:

- 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: SR.

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–present), PubMed (MEDLINE) (1966–2023), Virtual Health Library (1982–2023), Cochrane Central Register of Controlled Trials (Cochrane), Trip Database, Scopus, Web of Science and Cumulative Index to Nursing and Allied Health Literature. The search will use the following MeSH (Medical Subject Headings) 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 online supplemental 1. We will include articles published up to 17 August 2023. To remove duplicate studies before screening, the search results will be exported to EndNote V.X9 (Clarivate Analytics).

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, will be used as an auxiliary tool for archiving, organising and selecting the studies.

Data extraction

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

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

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

SR: risk of bias

For each SR included in the study, the ROBIS tool[29] will be applied, encompassing three assessment phases (1: assessment of relevance; 2: identification of potential risks of bias during the review process; and 3: assessment of the overall risk of bias). Phase 2 consists of four domains (1: studies' eligibility criteria; 2: studies' identification and selection; 3: data collection and studies' evaluation; and 4: synthesis and results). The results of the risk of bias assessment are categorised 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.

SR: 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 categorised 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 the evidence presented by each SR for every outcome of interest. We will follow the 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 do 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 PRIOR statement.[27] Additionally, the GRADE Summary of Findings tables will be employed to summarise 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 protocol.

Data set statement

Research data associated with this study will 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 systematic approach involving identification, appraisal and synthesis of multiple SRs 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, better offering 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, signalling 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 AMSTAR 2[28] and ROBIS[29] will enable health decision-makers to identify high-quality SRs, even those based on observational studies, of metformin use in pregnant women with PCOS. Recognising the importance of 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 postcompletion 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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Contributors 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 DSN are leading the design of the database search strategies. DSN, BLJ, BAS and JFA wrote the first draft of the manuscript. LT reviewed the methods 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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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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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	7
	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)	
	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.