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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.

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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.

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