BMJ Open

Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis

Han Yang ,[1] Yan-qun Xiao,[2] Jia-jia Liu,[1,3] Gui-xing Xu,[1] Juan Li ,[4] Zhi-yong Xiao,[1] Jun Zhou,[1] Xiao-yan Zheng ,[1,3] Li-ying Liu ,[1] Zheng Yu,[5] Jie Yang,[1,3] Fan-rong Liang [1]

To cite: Yang H, Xiao Y, Liu J, *et al*. Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e059090. doi:10.1136/bmjopen-2021-059090

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059090).

HY, Y-qX and J-jL contributed equally.

Received 08 November 2021
Accepted 19 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Fan-rong Liang;
acuresearch@126.com

ABSTRACT

Introduction Most overweight/obese women with polycystic ovary syndrome (PCOS) have infertility issues which are difficult to treat. Non-pharmacological interventions used for the management of infertility include lifestyle interventions, acupuncture therapies and nutritional supplements. These interventions have been reported to be beneficial in alleviating infertility among overweight women with PCOS. However, effect and safety of these non-pharmacological interventions vary, and there is no standard method of clinical application. Therefore, it is necessary to conduct a systematic review and network meta-analysis (NMA) to rank these non-pharmacological interventions in terms of effect and determine which one is more effective for clinical application.

Methods and analysis We will retrieve eight databases including Cochrane Library, Medline, Embase, PsycINFO, Chinese National Knowledge Infrastructure, WanFang Data, the Chongqing VIP Database and China Biology Medicine disc from their inceptions onwards. In addition, four clinical trial registries and the related references will be manually retrieved. The primary outcome will be clinical pregnancy. Live birth, ovulation, pregnancy loss, multiple pregnancy and adverse events related to interventions will be considered as the secondary outcomes. STATA software V.15.0 and Aggregate Data Drug Information System V.1.16.8 will be used to conduct pairwise meta-analysis and NMA. The Grading of Recommendations Assessment, Development and Evaluation system will be adopted to evaluate the certainty of evidence.

Ethics and dissemination Ethical approval will not be required because the study will not include the original information of participants. The results will be published in a peer-reviewed journal or disseminated in relevant conferences.

PROSPERO registration number CRD42021283110.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first study to comprehensively compare efficacy and evaluate safety of different non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome (PCOS) and their effects on ovulation and pregnancy outcomes using Bayesian network meta-analysis.
⇒ The certainty of evidence will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation system.
⇒ The study will focus on commonly used non-pharmacological interventions, such as lifestyle interventions, acupuncture therapies and nutritional supplements, which may lead to limitations to application of the findings for clinical guidance.
⇒ The population will be restricted to overweight/obese PCOS patients, which may limit the extrapolation of the findings to other populations.
⇒ Different protocols of the same intervention will not be compared in this study; the optimal protocol of the intervention remains to be further investigated.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic and reproductive disorder characterised by anovulation, hyperandrogenism and polycystic ovarian morphology.[1 2] PCOS affects approximately 5%–20% of women of reproductive age worldwide[3 4] and is the main cause of infertility.[5] It was estimated that the economic burden of PCOS was US$8 billion annually in 2020.[6] Overweight and obese patients account for a significant proportion of women with PCOS.[7] For example, approximately 37% of patients diagnosed with PCOS in China are overweight or obese.[8] Obesity can further aggravate metabolic and reproductive disorder of women with PCOS.[9] For instance, it can

increase insulin resistance and androgen levels, further impairing ovarian function. Moreover, obesity can increase the incidence of anovulation and menstrual disorders, and lower sensitivity of clomiphene and gonadotropin to ovulation, making treatment more difficult, and imposing a serious burden to the families and the whole society.[10]

Studies have explored a variety of interventions in overweight/obese women with PCOS to maximise ovulation and pregnancy outcomes, including pharmacotherapy, non-pharmacological interventions and surgery. A previous study reported that non-pharmacological interventions were effective in improving ovulation and pregnancy outcomes.[11] Currently, lifestyle interventions have been recommended as the first line of treatment for patients with PCOS, especially for overweight/obese PCOS according to guidelines.[12] Notably, preconception lifestyle changes are beneficial to weight loss and improve ovulation rates.[13] There is a growing concern on the efficacy of acupuncture therapy. It has been reported that acupuncture could improve recovery of menstrual cycles and decrease the levels of body mass index in women with PCOS.[14] Several studies report that nutritional supplements are able to alleviate infertility in patients with PCOS.[15–17] A recent study has explored the effect of inositol in improving sex hormone binding globulin, dehydroepiandrosteronesulfate and testosterone levels compared with common pharmacological interventions.[18] However, studies are inconsistent in efficacy and safety of these non-pharmacological interventions. Therefore, it is challenging for decision-makers to choose non-pharmacological interventions.

Network meta-analysis (NMA) can be used for analysis of indirect and direct data to rank different interventions,[19 20] which realises the possibility of including randomised controlled trials (RCTs) that do not have a non-treatment or minimal treatment control group in the same analysis. The aim of the study is to compare the efficacy and evaluate the safety of common non-pharmacological interventions for overweight/obese women with PCOS and their role in improving ovulation and pregnancy outcomes through systematic review (SR) and NMA.

METHODS

Study registration

This protocol was registered on PROSPERO (CRD42021283110) and was reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement guidelines (online supplemental file 1 for PRISMA-P checklist).[21] The findings of this study will be presented following the checklist of items to include when reporting a systematic review involving a network meta-analysis (PRISMA-NMA).[22]

Inclusion criteria

Types of studies

Only RCTs presented in English or Chinese will be included in the study. Articles on parallel design RCTs and the first stage of cross-over RCTs will be retrieved.

Participants

Participants diagnosed with PCOS and overweight or obese will be included. Women who will either chose to undergo assisted reproductive technology (ART) or conceive naturally will be enrolled. There will be no restrictions on age, race, nationality and education levels.

Types of interventions

Non-pharmacological interventions used as main treatment or main adjuvant treatment will be included. Non-pharmacological interventions will be limited to lifestyle interventions (including dietary intervention, exercise intervention and behavioural intervention), acupuncture therapies and nutritional supplements. Dietary intervention include calorie reduction or diet structure change (carbohydrate counting, fat counting, protein counting).[23] And exercise intervention include resistance or aerobic exercise.[23] Studies used single or multiple non-pharmacological intervention(s) will be considered.

Types of comparator(s)/control

Comparators will be ART, or western medicine, or usual care, or placebo, or sham interventions, or blank control, or other different non-pharmacological interventions.

Types of outcome measures

Primary outcomes

Clinical pregnancy will be considered as the primary outcome in the study. Clinical pregnancy will be defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation.[24] As for multiple intrauterine gestational sacs, it will be regarded as one clinical pregnancy.

Secondary outcomes

Live birth, ovulation, pregnancy loss and multiple pregnancy will be regarded as secondary outcomes. Live birth will be defined as live newborns beyond week 24 of gestation.[25] Multiple newborns at the same delivery will be counted as one live birth. Ovulation will be monitored by ultrasound or urine luteinising hormone strips. Pregnancy loss will include miscarriage, termination of pregnancy and perinatal mortality, which will be defined as any stillbirth or neonatal death in the first week of life excluding those due to congenital anomalies (chromosomal and/or structural) assessed via death certification.[26] Multiple pregnancy will be defined as carrying two or more fetuses in one pregnancy. Adverse events related to interventions will be used to evaluate safety.

Exclusion criteria

1. Design type is non-RCT.
2. Patients with other diseases that affect fertility.

3. Studies that compared different pharmacological interventions or surgeries between groups.
4. Duplicated studies.
5. Studies lacking the full text despite all efforts to obtain it.

Studies that meet any of the criteria above will be excluded.

Search methods for identification of studies

Articles will be retrieved from eight databases including four English databases (Cochrane Library, Medline, Embase and PsycINFO) and four Chinese databases (Chinese National Knowledge Infrastructure, WanFang Data, the Chongqing VIP Database and China Biology Medicine disc). Studies published from inceptions onwards will be retrieved. The literature search will be conducted using search terms such as "non-pharmacological intervention", "obesity", "PCOS" and "RCT" based on the principle of subject words combined with free words. Appropriate adjustments will be made according to different database. A specific searching strategy is presented in table 1 using Medline as example.

Data collection and analysis

Selection of studies

Endnote software V.9.1. will be used to manage the retrieved studies and remove duplicates. Two independent researchers (J-jL and Z-yX) will screen the studies by reading the titles and abstracts, according to the eligible criteria. Then, second screening will be conducted by reading the full text. The reasons for exclusion will be recorded. The included studies will be cross-checked. The two researchers will hold a discussion in case of any dispute to reach an agreement. A third researcher (F-rL) will be consulted if the disagreement will not be resolved through discussion. The selection procedure is presented in a PRISMA flow chart (figure 1).

Data extraction and management

Two researchers (HY and JZ) will independently extract data based on a predesigned form. The extracted data will be as followed: (1) basic information (name of the first author, year of publication, country, study type, sample size, number of centres, sources of funds and conclusion); (2) participants (age, diagnostic criteria and course of disease); (3) interventions (intervention type, details of intervention and intervention session/frequency/duration/dosage); (4) controls (control type, details of control and treatment session/frequency/duration/dosage); (5) outcomes (data for each measurement and safety). The corresponding authors will be contacted for missing information. The two researchers will cross-check the data after completion of data extraction. The disagreements will be solved by the team discussion or consultation with the third researcher (F-rL).

Assessment of risk of bias

Two independent researchers (Y-qX and G-xX) will assess the risk of bias (ROB) of included studies using

Table 1 Search strategy for Medline (through Ovid).

Number	Search items
1	exp Polycystic Ovary Syndrome/
2	polycystic ovar$.tw.
3	PCOS.tw.
4	PCOD.tw.
5	hirsut$.tw.
6	exp Amenorrhea/ or exp Oligomenorrhea/ or exp Hirsutism/
7	oligomenorrh$.tw.
8	amenorrh$.tw.
9	or/1–8
10	(Obesity or obese or overweight).tw.
11	exp Obesity/ or exp Overweight/ or exp Body Weight/
12	exp Body Composition/ or exp Body Fat Distribution/
13	exp Body Mass Index/
14	(High BMI or BMI above).tw.
15	(BMI adj3 over).tw.
16	Body Mass Index.tw.
17	or/10–16
18	exp Diet Therapy/
19	diet$.tw.
20	exp Weight Loss/
21	(weight adj2 lose).tw.
22	Weight Loss.tw.
23	(weight adj3 reduc$).tw.
24	((body mass index adj2 loss) or reduc$ or decreas$).tw.
25	((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas$)).tw.
26	exp Exercise Therapy/
27	(exercise$ or exercising).tw.
28	exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/
29	(run$ or jog$).tw.
30	(sport$ or walk$).tw.
31	swim$.tw.
32	train$.tw.
33	fitness.tw.
34	yoga.tw.
35	exp cognitive therapy/ or exp relaxation techniques/
36	(cognitive adj2 therap$).tw.
37	exp Psychotherapy/
38	Psychotherapy.tw.
39	psychosocial.tw.
40	exp Behavior Therapy/

Continued

Table 1 Continued

Number	Search items
41	(Behavio?r adj2 therap$).tw.
42	behavio?r modif$.tw.
43	(behavio?r adj2 manage$).tw.
44	CBT.tw.
45	exp life style/ or exp life change events/
46	((life*style adj2 change$) or intervention$).tw.
47	counselling.tw.
48	social support/
49	(social adj2 support).tw.
50	relaxation.tw.
51	exp self efficacy/
52	self efficacy.tw.
53	exp Health Promotion/
54	(Health adj2 Promotion).tw.
55	exp Health Education/
56	(Health$ adj2 Education).tw.
57	(motivation$ adj2 therap$).tw.
58	acupuncture.tw.
59	exp Acupuncture/
60	exp acupuncture therapy/ or exp acupuncture, ear/ or exp electroacupuncture/ or exp meridians/ or exp acupuncture points/ or exp moxibustion/
61	electroacupuncture.tw.
62	meridian$.tw.
63	needling.tw.
64	moxi$.tw.
65	acup$ point$.tw.
66	(shiatsu or tui na).tw.
67	shu.tw.
68	acupressure.tw.
69	(trigger adj3 point$).tw.
70	oral nutritional supplement.mp.
71	exp *Dietary Supplements/
72	exp *Nutritional Support/
73	or/18–72
74	randomized controlled trial.pt.
75	controlled clinical trial.pt.
76	randomized.ab.
77	randomised.ab.
78	placebo.tw.
79	clinical trials as topic.sh.
80	randomly.ab.
81	trial.ti.
82	(crossover or cross-over or cross over).tw.
83	or/74–82
84	exp animals/ not humans.sh.
85	83 not 84
86	9 and 17 and 73 and 85

Moreover, clinical trial registries will be searched for relevant ongoing trials and unpublished trials including the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), the National Institutes of Health clinical registry ClinicalTrials.gov (https://www.clinicaltrials.gov/), the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and the Chinese clinical registry http://www.chictr.org/en/. References in all identified publications will be searched manually. In addition, experts in this field will be consulted for eligible studies.
BMI, body mass index.

the Cochrane Collaboration's tool for assessing ROB V.2.0.[27 28] The following five domains will be evaluated: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in outcome measurement and (5) bias in selection of the reported result. The overall bias will be considered *low ROB* if all domains will be marked *low risk*. The overall bias will be expressed as having *some concerns* if one domain will be denoted as *some concern*. The overall bias will be *high ROB* if one domain will be marked *high risk* or several domains will be denoted as *some concern* and may influence the robustness of the study. Corresponding authors will be contacted if there is any missing information that would affect the assessment. The two researchers will cross-check the data after completion of assessments. The two researchers will

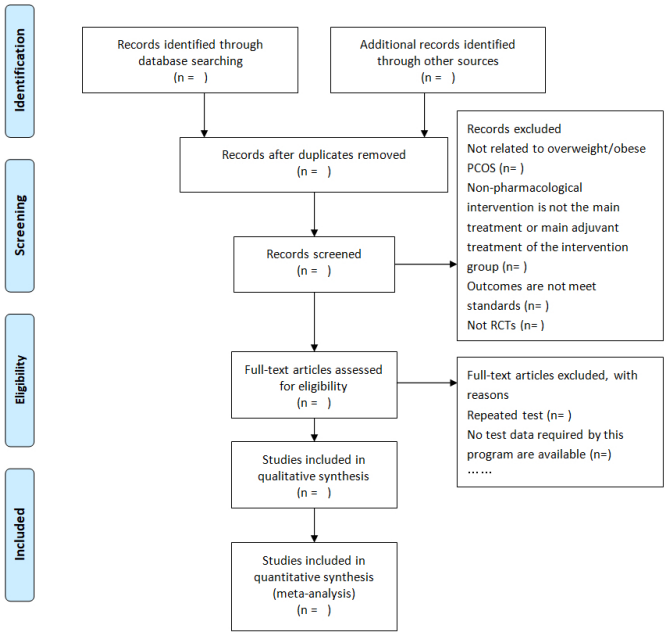

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the study selection process. PCOS, polycystic ovary syndrome; RCTs, randomised controlled trials.

hold a discussion if any dispute occurs to reach an agreement. A third researcher (F-rL) will be consulted if the two researchers will not reach a consensus.

Evaluation of certainty of evidence

Two independent researchers (JL and ZY) will evaluate the certainty of evidence of each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[29] The certainty of evidence will be rated as *high*, *moderate*, *low* or *very low* based on the rating criteria recommended in GRADE. Two researchers will cross check the results after evaluation of the certainty of evidence. Any dispute will be solved through discussion or a third researcher (F-rL) will be consulted.

Assessment of similarity and consistency

Similarity and consistency will be evaluated to obtain valid and credible results. Similarity will be assessed according to clinical characteristics and methodological characteristics owing to the challenges in clarifying similarity by statistical analysis. Study designs, participant characteristics and interventions will be included in the assessment. Local inconsistency will be evaluated using the node splitting method. P>0.05 indicates no statistical significance implying that it is consistent to the direct and indirect comparison. P<0.05 represents statistical significance indicating inconsistency. A consistency model or inconsistency model will be chosen based on the results. Potential scale reduced factor (PSRF) will be used to determine convergence. PSRF close to 1 indicates successful convergence.

Pairwise meta-analysis

STATA software V.15.0 (Stata Corp LP) will be used for data analysis. Statistical heterogeneity will be evaluated by calculating the I^2 value. I^2<50% indicates that the heterogeneity is acceptable. Otherwise, heterogeneity will be considered as significant. The random-effects model will be chosen in consideration of the suggestion that it is generally a more plausible match.[30] Descriptive review will be adopted if the heterogeneity is significant. Since clinical pregnancy, live birth, ovulation, pregnancy loss and multiple pregnancy are dichotomous outcomes, risk ratio will be used to synthesise the pooled data.

Network meta-analysis

Aggregate Data Drug Information System (V.1.16.8, Drugis, Groningen, Netherlands) and Markov Chain Monte Carlo method will be used for Bayesian network analysis to synthesise data.[31] In addition, STATA software V.15.0 will be used to compare different interventions of each outcome and forest plots will be generated to present the NMA results. The rank of various non-pharmacological interventions will then be generated. Comparisons between interventions will be presented as a network plot and the contribution of different designs to the final effect size of the NMA will be presented as rank plots. Non-pharmacological interventions will be ranked based on the p score, which determined whether the extent of certainty when the intervention group is superior compared with the control group. A p of 100% indicates that the treatment is better relative to the control whereas p value of 0% indicates that the treatment worse compared with the control.

Subgroup analysis, metaregression analysis and sensitivity analysis

Subgroup analysis and metaregression analysis will be conducted to explore the possible sources of heterogeneity and inconsistency. If data are available, subgroup analysis will be performed based on different types of non-pharmacological interventions and metaregression analysis will be performed based on the duration of PCOS, the degree of obesity, the age of patients, country of origin of patients, whether ART has been used, and dose of intervention. In addition, sensitivity analysis will be conducted by excluding one study by one study to verify the robustness of the results.

Publication bias assessment

A comparison-adjusted funnel plot will be generated to detect the reporting bias if more than 10 studies will be included.

Patients and public involvement

The study will be an SR and NMA based on existing studies; therefore, no patients or public will be involved directly.

DISCUSSION

To the best of our knowledge, this will be the first SR and NMA study to compare the efficacy and safety of non-pharmacological interventions in overweight/obese women with PCOS based on ovulation and pregnancy outcomes. The findings from the study will provide a ranking of non-pharmacological interventions to help patients, doctors and policy-makers for decision-making. In addition, the GRADE will be adopted to evaluate the certainty of evidence. There will be also some limitations of the study. First, non-pharmacological interventions in PCOS are an extensive research field, but we only focus on lifestyle interventions, acupuncture therapies and nutritional supplements,[11] which may lead to limitations of clinical practice. Second, considering that overweight/obese patients have an increased risk of metabolic disorders[32] and tend to benefit more from non-pharmacological interventions compared with normal weight patients, we will restrict the population to overweight/obese PCOS, which may limit the extrapolation of the conclusion. Third, the efficacy of different protocols of the same non-pharmacological intervention will not be investigated.

Ethics and dissemination

The study will not require ethical approval because it comprises analysis based on existing studies. The results are expected to be published in a peer-reviewed journal

or disseminated at relevant conferences. The findings will provide evidence on use of non-pharmacological interventions for overweight/obese women with PCOS and the effect on ovulation and pregnancy outcomes thus promoting the clinical application of these methods.

Author affiliations
[1]Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China
[2]Infertility Clinic, Chengdu Xinan Gynecological Hospital, Chengdu, China
[3]Traditional Chinese Medicine Department, Chengdu Xinan Gynecological Hospital, Chengdu, China
[4]School of Health Preservation and Rehabilitation, Traditional Chinese Medicine of Chengdu University, Chengdu, Sichuan, China
[5]College of Medical Information and Engineering, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Contributors HY conceived the review protocol and drafted the manuscript. JL, JY and F-rL revised the study design. HY, Y-qX, JZ, J-jL, Z-yX, L-yL and ZY participated in the design of the search strategy and data extraction dataset. Y-qX, G-xX, L-yL, X-yZ and HY formed the data synthesis and analysis plan. In practice, JY and F-rL will monitor each procedure of the review and be responsible for quality control. All authors have read and approved the publication of the protocol.

Funding This study will be supported by grants from the National Natural Science Foundation of China (82174517) and the National Natural Science Foundation of China (82074556).

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 applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Han Yang http://orcid.org/0000-0002-0939-2392
Juan Li http://orcid.org/0000-0002-8530-9001
Xiao-yan Zheng http://orcid.org/0000-0002-2740-7076
Li-ying Liu http://orcid.org/0000-0001-8943-6203
Fan-rong Liang http://orcid.org/0000-0001-8518-9268

REFERENCES

1 Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocr Rev* 2016;37:467–520.
2 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19–25.
3 Azziz R. Polycystic ovary syndrome. *Obstet Gynecol* 2018;132:321–36.
4 Azziz R, Carmina E, Chen Z, *et al*. Polycystic ovary syndrome. *Nat Rev Dis Primers* 2016;2:16057.
5 Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol* 2004;18:671–83.
6 Riestenberg C, Jagasia A, Markovic D, *et al*. Health Care-Related economic burden of polycystic ovary syndrome in the United States: pregnancy-related and long-term health consequences. *J Clin Endocrinol Metab* 2022;107:575–85.
7 Ehrmann DA, Barnes RB, Rosenfield RL, *et al*. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;22:141–6.
8 Zhang HY, Guo CX, Zhu FF, *et al*. Clinical characteristics, metabolic features, and phenotype of Chinese women with polycystic ovary syndrome: a large-scale case-control study. *Arch Gynecol Obstet* 2013;287:525–31.
9 Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med Overseas Ed* 2005;352:1223–36.
10 Lim CED, Ng RWC, Cheng NCL, *et al*. Acupuncture for polycystic ovarian syndrome. *Cochrane Database Syst Rev* 2019;7:Cd007689.
11 Pundir J, Charles D, Sabatini L, *et al*. Overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome. *Hum Reprod Update* 2019;25:243–56.
12 Teede HJ, Misso ML, Deeks AA, *et al*. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 2011;195:S65–112.
13 Legro RS, Dodson WC, Kris-Etherton PM, *et al*. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2015;100:4048–58.
14 Jo J, Lee YJ, Lee H. Acupuncture for polycystic ovarian syndrome: a systematic review and meta-analysis. *Medicine* 2017;96:12–18.
15 Thakker D, Raval A, Patel I, *et al*. N-Acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Obstet Gynecol Int* 2015;2015:1–13.
16 Fang F, Ni K, Cai Y, *et al*. Effect of vitamin D supplementation on polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Clin Pract* 2017;26:53–60.
17 Pundir J, Psaroudakis D, Savnur P, *et al*. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. *BJOG: Int J Obstet Gy* 2018;125:299–308.
18 Abdel-Maboud M, Menshawy A, Hasabo EA, *et al*. The comparative effectiveness of 55 interventions in obese patients with polycystic ovary syndrome: a network meta-analysis of 101 randomized trials. *PLoS One* 2021;16:e0254412.
19 Chaimani A, Higgins JPT, Mavridis D, *et al*. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654.
20 Salanti G, Del Giovane C, Chaimani A, *et al*. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682.
21 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
22 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
23 Kim C-H, Lee S-H. Effectiveness of lifestyle modification in polycystic ovary syndrome patients with obesity: a systematic review and meta-analysis. *Life* 2022;12. doi:10.3390/life12020308. [Epub ahead of print: 18 02 2022].
24 Latif S, Wattar BHA, Balachandren N, *et al*. Effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (ModA) study protocol: a pragmatic randomised-controlled trial. *BMJ Open* 2021;11:e050248.
25 Rikken JFW, Kowalik CR, Emanuel MH, *et al*. The randomised uterine septum transsection trial (trust): design and protocol. *BMC Womens Health* 2018;18:163.
26 Hodgetts-Morton V, Hewitt CA, Jones L, *et al*. C-STICH2: emergency cervical cerclage to prevent miscarriage and preterm birth-study protocol for a randomised controlled trial. *Trials* 2021;22:529.
27 Cumpston M, Li T, Page MJ, *et al*. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019;10:Ed000142.
28 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
29 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.

30 Borenstein M, Hedges LV, Higgins JPT, *et al*. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97–111.
31 Cipriani A, Higgins JPT, Geddes JR, *et al*. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159:130–7.
32 Liu C, Zhang L, Zheng W, *et al*. Lifestyle intervention for overweight/obese pregnant women with polycystic ovarian syndrome: lessons and challenges. *Obes Facts* 2021;14:405–14.

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	Reported on Page Number/Line Number	Reported on Section/Paragraph
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Page 1/Line 2-3	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2/Line 56	Abstract
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1/Line 4-17	Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 12-13/Line 307-313	Contributions
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	N/A	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Page 13/Line 314-317	Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	N/A
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4/Line 89-105	Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4/Line 109-112	Introduction
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	Page 4-6/Line 121-160	Methods/ Inclusion criteria
Information	9	Describe all intended information sources (such as electronic databases, contact with study authors,	Page 6,8/Line 170-	Methods/ Search

sources		trial registers or other grey literature sources) with planned dates of coverage	178,181-187	methods for identification of studies
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	Page 6-8/Line 179	Methods/ Table 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 9/Line 190-191	Methods/ Data collection and analysis/ Selection of studies
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)	Page 9/Line 191-197	Methods/ Data collection and analysis/ Selection of studies
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	Page 9/Line 199-209	Methods/ Data collection and analysis/ Data extraction and management
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	Page 9/Line 200-207	Methods/ Data collection and analysis/ Data extraction and management
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6/Line 144-160	Methods/Inclusion criteria/Types of outcome measures
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	Page 9-10/Line 211-225	Methods/ Assessment of risk of bias

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 10-11/Line 246-253	Methods/ Pairwise meta- analysis
	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)	Page 10/Line 235-244	Methods/ Assessment of similarity and consistency
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 11/Line 268-274	Methods/ Subgroup analysis, meta-regression analysis, and sensitivity analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 11/Line 251	Methods/ Pairwise meta- analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 11/Line 276-277	Methods/ Publication bias assessment
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10/Line 227-233	Methods/ Evaluation of certainty of evidence

*** 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.