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Comparison of the effect of dietary and herbal supplements on anthropometric, metabolic and androgenic profiles of women with polycystic ovary syndrome: a systematic review and network meta-analysis protocol

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Abstract

Polycystic ovarian syndrome (PCOS) is characterized by obesity, glucose intolerance, dyslipidemia, and hyperandrogenemia. Although several, placebo-controlled 2x2 factorial design, randomized controlled trials have tested the efficacy of dietary and herbal supplements in controlling these parameters in PCOS patients, these studies are not suitable for a comparative efficacy assessment across these supplements. Herein, a protocol for systematic review and network meta-analysis (NMA) is presented to make such a comparison. PubMed, Embase, and Scopus, were interrogated to identify relevant trials, published in English, factors to be investigated will include dietary factors, micronutrients, choline, essential fatty acids, and herbal extracts. Other factors to be considered include trial design, population characteristics, interventions compared, and outcomes of interest. The revised Cochrane tool was used for the appraisal of eligible trials. NMA (frequentist method) will be used for respective outcomes to compare effect sizes (weighted or standardized mean difference) among the interventions. Both logical and statistical (inconsistency assessment) approaches will be used to minimize intransitivity risk. The surface under the cumulative ranking curve values will be used to gauge the best intervention for outcomes with a statistically significant effect size suggesting a favorable outcome. Additionally, the exploration of interrelation among interventions and the small study effect in respective NMA models will be investigated using network maps and comparison-adjusted funnel plots, respectively. Statistical significance is assumed at $p<0.05$ with 95% confidence interval. Stata statistical software (v16) was used for analysis. The study was registered with PROSPERO, registration number: CRD42022301530. (J Turk Ger Gynecol Assoc 2023; 24: 277-83)

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinological disorder of reproductive-age females. Depending on the diagnostic criteria used, its prevalence ranges between 5-15% (1). PCOS is a constellation of diverse clinical features, among which obesity, metabolic abnormalities, and hyperandrogenism are central (1). Pathophysiologically, these features are interconnected, and one can aggravate the other. Epidemiological and genetic studies suggest an intricate association between PCOS and obesity, which is not fully understood (2). Obesity in women with PCOS increases the risk of hyperandrogenemia, via insulin resistance (IR) (1), infertility (particularly with abdominal obesity) (3), and preterm births (4). In terms of metabolic abnormalities, IR is a major metabolic complication in patients with PCOS. Nearly

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two-thirds of PCOS patients have abnormal IR (1). IR-led hyperinsulinemia increases the risk of type 2 diabetes mellitus (T2DM) and impaired glucose tolerance in women with PCOS (1,5,6). Dyslipidemia is another key metabolic derangement in PCOS and can present with low levels of high-density lipoprotein (HDL) and high levels of triglyceride and low-density lipoprotein (LDL) (7-9). Hyperandrogenism in patients with PCOS is also associated with IR. IR-led hyperinsulinemia decreases sex hormone-binding globulin (SHBG) levels, which in turn increases the peripheral availability of free androgen and its consequent peripheral action (7). Hyperandrogenism can present clinically with hirsutism, acne, virilization, infertility, and alopecia (10). The biochemical presentation of hyperandrogenism includes elevated levels of testosterone, high free androgen index [(FAI) defined as the testosterone to SHBG ratio], and increased adrenal androgens, such as dehydroepiandrosterone sulfate (DHEAS) (10).

Contemporary treatments and their limitations

Presently, there is no cure for PCOS, and the treatment is symptom-directed (7). For weight loss and IR, the treatment choices include life style modification, bariatric surgery, weight loss-inducing drugs, and insulin-sensitizing drugs. Hormonal contraceptives are used for androgen-related symptoms. However, these PCOS managements are not supported by rigorous evidence and are often expert consensus-based and may not be suitable for all patients with PCOS. Although the consensus favors hypocaloric diet consumption for weight loss in PCOS patients, evidence remains unclear if any particular dietary formulation benefits weight loss or metabolic changes (7,11,12). Moreover, nearly 95% of PCOS patients undergoing weight loss experience relapse (7). A 2019 Cochrane review of randomized controlled trials (RCTs) reported a modest dip in body weight and body mass index (BMI) with lifestyle interventions (13). However, the reviewers categorized the evidence as low quality due to the high or unclear risk of bias (RoB) in the reviewed trials (13).

While it is believed that the benefits of exercise in PCOS patients are the same as in women with T2DM, there is no robust evidence in PCOS (7). Moreover, exercise is not an option for PCOS patients with locomotor disabilities. Despite the growing popularity of bariatric surgery for weight loss, it is presently of limited use for overweight and obese women with BMI ≥40 kg/m^2 (14), and many cannot afford it, if not available in national health programmes (15). In terms of weight loss-inducing drugs, there are inadequate efficacy data and safety concerns with certain drugs, such as Sibutramine and Rimonabant, which are not endorsed in the USA (7,16,17).

Among the insulin-sensitizing drugs, metformin is the only insulin-sensitizing drug recommended in PCOS, in patients not suffering from T2DM (18). Although metformin helps with weight loss, reducing IR, and mildly improving androgen-related symptoms (1), its role in diabetes prevention in patients with PCOS is not well-established due to the shortage of adequately powered studies of long duration (7).

While oral contraceptive pills are used for controlling androgenic effects, these are not ideal in women with PCOS who are planning to conceive or those with a history of smoking, obesity, hypertension, or clotting disorders (7).

The purpose of this study

Given these limitations of contemporary PCOS management, research for novel alternative or adjunct therapies are essential. Several RCTs have investigated the role of various dietary supplements and herbal extracts on the anthropometric, metabolic, and androgenic markers in PCOS. For instance, trials in PCOS patients testing the role of chromium (19), cinnamon (20), Salvia officinalis extract (21), and flaxseed (22) supplementation improved certain glycemic and lipid parameters, such as insulin levels and LDL concentrations, respectively. The trials supplementing cinnamon (20) and flaxseed (22) in PCOS found no significant decrease in testosterone levels, but quercetin (23) supplementation was reported to decrease testosterone levels. However, the comparative efficacy of these supplements remains unclear, due to the 2x2 placebo-controlled factorial design of such trials. An across-supplement comparison would allow healthcare professionals to choose the optimal supplement or supplement mix for controlling clinical and biochemical parameters of interest in PCOS patients and deliver more patient-specific care.

Therefore, this systematic review and network meta-analysis (NMA) protocol was performed and the results are presented here to juxtapose the efficacy of various dietary supplements and herbal extracts in controlling body weight, BMI, waist circumference, markers of blood glucose and lipid metabolism and androgenic markers. A complete list of interventions and outcomes of interest are listed below. The protocol for this proposed systematic review is presented below.

Methods

The protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (2015) guidelines (Supplement 1) (24). This protocol was registered with PROSPERO (registration no: CRD42022301530) (25).

Eligibility criteria

Inclusion criteria

a. Trial population: Women of any age with PCOS. The diagnosis of PCOS will get accepted as per the trialists.

b. Trial design: Irrespective of treatment duration and the number of intervention arms, parallel-arm RCTs were eligible for inclusion.

c. Intervention arm: Women in the treatment arm/s should have been receiving at least one of the following oral interventions;

1. Dietary factors: L-carnitine, coenzyme Q10, lipoic acid, probiotics, synbiotics, and phytochemicals will be included. The following phytochemicals will be considered-chlorophyll and chlorophyllin, carotenoids, curcumin, garlic, indole-3-carbinol isothiocyanates, fiber (such as psyllium or included with prebiotics), phytosterols, flavonoids (e.g. quercetin), soy isoflavones, lignans, resveratrol.
2. Micronutrients to be considered include: water- and fat-soluble vitamins and minerals such as calcium, copper, selenium, chromium, iron, magnesium, manganese, molybdenum, phosphorus, iodine, potassium and zinc.
3. Choline.
4. Essential fatty acids (e.g. omega-3 fatty acids).
5. Herbal extracts (e.g. thylakoid).

The dosage and regimen of these interventions, as stated by the trialists, will be accepted. Trial participants receiving a combination of these supplements will also qualify.

d. Comparator arm: The control arm must receive standard PCOS care (with or without placebo).

e. Outcomes:

1. Glycemic markers: fasting plasma glucose, homeostasis model assessment of IR, insulin, glycated hemoglobin, and quantitative insulin sensitivity check index.
2. Lipid markers: HDL, LDL, and very LDL, triglyceride, and total cholesterol.
3. Anthropometric indices: weight, BMI, and waist circumference.
4. Sex hormones: DHEAS, follicle-stimulating hormone, luteinizing hormone, testosterone, SHBG and FAI.

The above list of interventions and outcomes of interest cannot be exhaustive because trialists continue testing newer supplements and biochemical markers. Therefore, this list was prepared based on prior knowledge and scrutiny of relevant contemporary trials (accessible utilizing the pilot search strategy depicted below). Preparation of the outcomes list was based on clinical relevance in PCOS. However, given the large number of interventions and outcomes that may be tested in different future clinical trials, we will include additional relevant interventions and outcomes that emerge during the study selection stage of the review.

Exclusion criteria

a. Trials in pregnant or lactating females.

b. Trials in women with endocrinopathies mimicking PCOS (e.g., Cushing's syndrome, androgen-producing tumors, non-classic adrenal hyperplasia, and pharmacologically induced androgen excess).

Information sources and search strategy

We will search for eligible trials published in the English language in the PubMed, Scopus, and Embase databases since the conception of these databases, irrespective of the publication date and geographic origin of the study. A draft search string for searching the PubMed database is as follows: ("polycystic ovary*"[Title/Abstract] OR "PCOS"[Title/Abstract] OR "stein leventhal"[Title/Abstract] OR "stein leventhal"[Title/Abstract] OR "Sclerocystic Ovarian"[Title/Abstract] OR "Ovarian Degeneration"[Title/Abstract] OR "Sclerocystic Ovaries"[Title/Abstract]) AND (controlledclinicaltrial[Filter]). This search string was considered appropriate (26) as it retrieved five, pre-identified eligible citations (Supplement 2) (19-23). Using identical search strings, the other databases will also be interrogated. Supplementary searches will take place in the bibliography of the articles included in the review.

After uploading the retrieved citations into Rayyan, a systematic reviewing software, duplicate citations will be excluded, and then, the remaining articles' titles and abstracts will be skimmed for eligibility (27). A full-text reading will occur for articles that may be icluded or those deemed unlikely to be included. A list of excluded articles will be kept, following the full-text reading and the list will include reasons for exclusion.

Data abstraction

The following data items will be abstracted, primarily in a data abstraction form (weblink):

1. The following study details will be collected for each trial: first author's last name, date of publication, country of conduct, single or multicentered, trial identification details, ethics information, participant consent, and funding sources.
2. Characteristics of the study population to be collected will include**:** The number of PCOS patients in each intervention arm and their ages, the diagnostic criteria used to diagnose PCOS, BMI of participants in respective intervention arms, and the PCOS treatment participants were receiving in addition to the interventions being tested.
3. The intervention tested in the respective treatment arms of the reviewed trials will be noted, along with dosage, frequency of administration, and duration of intake.
4. In the data abstraction form (weblink), outcomes of interest for which the trialists reported outcome data will be recorded. In a separate form, analytic data gathering will happen from respective trial arms (Supplement 3).

Risk of bias in individual studies

The RoB assessment will be performed for respective studies using the Revised Cochrane RoB 2 tool for randomized trials (28). Signaling questions assessing the following domains will be answered to determine their bias: the method of randomization, interventions aimed to be studied, unavailable outcome data, measurements of the outcome data, and reported results. The review authors will assess the appropriateness of the electronic algorithm-generated bias for each of the domains and modify it if they feel necessary. An overall assessment will be performed for each study, based on the judgment made for respective domains (described elsewhere) (28).

Three or more authors will perform the review. They will carry out study selection, data abstraction, and the RoB assessment individually, and subsequently collate their findings. All conflicts in an opinion between review authors will be resolved by discourse and a third-party opinion will be sought if the latter doesn't achieve consensus.

Network meta-analysis

Using the endpoint average and their standard deviations (SD), we will conduct NMA (frequentist methods) to compare treatment effects across the interventions. The NMA models will source data from trial arms that have tested a combination of supplements in these combined forms so that these interventions can be contrasted with other mono- or co-supplemented forms. For instance, vitamin D sole administration and vitamin D-calcium simultaneous administration forms will be included in the NMA models in these respective forms and not as a unique vitamin D supplementation group.

Outcome selection criteria for network meta-analysis

An outcome will be considered eligible for NMA when it meets the criteria listed below (26,29,30):

1. Low heterogeneity: Outcomes for which a pairwise meta-analysis (PMA)-based comparison between intervention recipients and non-recipients suggest low heterogeneity risk will be incorporated in the NMA models. Heterogeneity detection and quantification will be made using Chi^2 statistics (statistically significant at $p<0.1$) (31) and I^2 values (of which 25, 50, and 75% are interpreted as low, moderate, and high heterogeneity, respectively) (32).

This statistical inconsistency evaluation will occur if these PMA models include a minimum of 20 studies or an average study population size of ≥80 (for adequately powered (80%) analysis) (33). The meta-analysis model choice, fixed-effect versus random-effect (DerSimonian and Laird), will depend on the methodological diversity among the trials included in the review, and an appraisal of this will include consideration of features such as baseline demographic characteristics, treatment duration, the design and setting of the clinical trials, and PCOS-diagnostic criteria.

We will combine the endpoint means and their SDs across intervention arms of trials testing the effect of dietary supplements in >1 intervention arm using equations (31) 1 and 2-

$$\text{Mean} = \frac{(n1m1+n2m2)}{n1+n2} \quad (1)$$

$$\text{SD} = \sqrt{\left(((n1-1)sd1^2)+\left((n2-1)sd2^2\right)+\left(\frac{n1n2}{n1+n2}\right)(m1^2+m2^2-2m1m2)\right)/((n1+n2)-1)} \quad (2)$$

where,

n1, n2: sample sizes of hypothetical sample sizes of treatment arm 1 and treatment arm 2, respectively,

m1, m2: average value of treatment arm 1 and treatment arm 2, respectively,

sd1, sd2: SD of m^1 and m^2, respectively.

2. A connected network must be formed for each outcome.

3. The heterogeneity's degree of freedom should allow a consistency model fitting (random effect).

4. The degree of freedom of the inconsistency should allow for an inconsistency model fitting.

We will perform a random-effect NMA to allow for heterogeneity as it is not possible to guarantee that the trials randomized by intervention will be exclusively identical in trial characteristics (e.g., study population characteristics or trial design) (34).

Transitivity and consistency

To ensure the validity of indirect comparisons (transitivity) when including several RCTs in an NMA model, we will check if the studies are identical in all aspects except the compared interventions (35-38).

To decrease intransitivity risk, the eligibility criteria of the proposed study are framed in such a manner that the trials are primarily different in the tested interventions only (38,39). For instance, as the bioavailability of the supplements and their consequent effect on the outcomes may vary with various routes of administration, trials using it in patients with PCOS and given orally will only get integrated in the proposed review. Similarly, trials in conditions mimicking PCOS will also not be selected.

The statistical transitivity assessment will include local and overall inconsistency evaluation (40). Network inconsistency resulting from transitivity assumption violation will be assessed using local and global inconsistency evaluations. The local node-splitting method will test inconsistency among respective intervention pairs (40). We will accept a network consistency assumption when both the local and overall inconsistency evaluations are suggestive of no inconsistency.

Network map

Using network maps, a visual assessment of the interventions compared in the NMA models will be undertaken. In each NMA model, the nodes will depict the interventions compared, and its width will increase as more trial participants receive it. The number of participants contributing to the formation of respective nodes of the network maps will be presented in tables. The node-connecting lines in the network map will depict the trials comparing two interventions (represented by nodes), which thickens as more trials compare these. If the network maps are too complex to interpret, due to excessive crisscrossing, we will attempt to decrease the intricacy by repeated swapping of treatment pairs (41).

Effect size

For PMA and NMA, the effect size estimation will be performed using weighted or standardized mean differences based on similarities or dissimilarities in reporting units across the trials, respectively (42).

A statistically significant effect size will determine the relative superiority among the compared interventions. A negative effect size will be considered favorable for an outcome in which a reduction in values is the anticipated outcome (e.g., fasting plasma glucose) and *vice versa*.

Obtaining SD in special circumstances

We will use formulas 3 or 4 to calculate SD from standard error or 95% CI, respectively (31).

$$SD = SE \times \sqrt{n} \quad (3)$$

$$SD = \sqrt{n} \times \frac{(\text{upper limit} - \text{lower limit})}{3.92} \quad (4)$$

where and SE are the sample size and standard error; 3.92 (2x1.96) SE was used for 95% confidence interval (CI); 3.29 and 5.15 can be used instead of 3.92, if reporting occurs at 90 or 99% CI, respectively (31). The CI values of 3.92, 3.29, or 5.15 will be substituted by slightly larger value derived from the specific t distribution when the respective treatment arms are made up of small sample sizes (n<60) (31).

League tables and ranking probabilities

In league tables, the effect sizes derived from the NMA of respective outcomes will be presented, with diagonal cells of these tables representing the interventions contained in the NMA models.

Our assessment of the best intervention will include the usage of the surface under the cumulative ranking curve values, which can range between 0-100%, with higher values representing superior interventions (43). This will be performed for outcomes with statistically significant effect sizes, as suggested by the league tables.

RoB across studies

As all trials included in the proposed review will compromise of a comparator arm receiving standard PCOS care with or without a placebo, the small study effect will be judged using comparison-adjusted funnel plots (44,45). Plots with asymmetry will suggest deviation in effect sizes among studies with large and small sample sizes (45).

Sensitivity analysis

The following sensitivity analysis will occur to ensure the robustness of the primary NMA:

1. If an NMA model included trials with a high RoB component, the repeat NMA will not incorporate these trials. It will help distinguish the latter's effect on the main NMA findings.
2. The NMA about androgenic markers will be iterated after eliminating trials conducted on menopausal women, as hyperandrogenism tends to resolve in PCOS patients nearing their menopause (46). Women ≥45 years will be considered in the menopausal age groups unless clarified in the trial (47).
3. As the method of diagnosis of PCOS remains unclear in pre-pubertal and peri-pubertal girls (5,7), preliminary analyses will be repeated following the exclusion of trials in women aged ≤19 years (as peri-puberty is up to adolescence, i.e., age 19 (48,49).
4. To evaluate if short duration trials (≤12 weeks) have affected the NMA findings, the NMA will be reiterated, eliminating any short duration trials.

Additional analysis

NMA will be performed for respective outcomes using data from trials with overweight and obese participants only, to disentangle the effects of dietary and herbal supplements in this patient population.

Risk of bias across studies

We will use comparison-adjusted funnel plots to assess publication bias. This assessment will be feasible as trials included in this review will have a common comparator arm receiving a placebo and/or standard care (50). Plots depicting asymmetry would indicate a variation between small and large RCTs (44,45).

Analytic tools

We will conduct the pairwise and NMA in the Stata statistical software version 16.0 (StataCorp, College Station, Texas, USA) using the meta and network packages, respectively, and determine the statistical significance of the effect sizes at a p-value of <0.05 and 95% CI.

Conclusion

Reporting of the review

The PRISMA statement for NMA will be followed for reporting of the completed review (51).

Confidence in cumulative evidence

We will determine the quality of the statistically significant NMA findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach proposed by the GRADE Working group (2004) (52), and categorized as high, moderate, low, and very low quality evidence.

Limitation

As review authors are knowledgeable in the English language only, reviewing articles in other languages will be beyond the scope of this proposed analysis. Limitations due to the use of NMA, such as heterogeneity and inconsistency, are plausible in the proposed review if heterogeneity across RCTs introduces bias in the pairwise comparisons and there is incongruence between direct and indirect effect estimates, respectively (53).

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References

1. Rasquin LI, Anastasopoulou C, Mayrin JV. Polycystic Ovarian Disease. 2022 Nov 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://pubmed.ncbi.nlm.nih.gov/29083730/
2. Barber TM, Hanson P, Weickert MO, Franks S. Obesity and polycystic ovary syndrome: implications for pathogenesis and novel management strategies. Clin Med Insights Reprod Health 2019; 13: 1179558119874042.
3. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update 2003; 9: 359-72.
4. De Frène V, Vansteelandt S, T'Sjoen G, Gerris J, Somers S, Vercruysse L, et al. A retrospective study of the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with polycystic ovary syndrome. Hum Reprod 2014; 29: 2333-8.
5. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015; 36: 487-525.
6. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989; 38: 1165-74.
7. Legro RS. Evaluation and treatment of polycystic ovary syndrome [Internet]. In: Feingold KR, Anawalt B, Boyce A et al., editor. Endotext [Updated 2017 Jan 11]; 2000. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25905194
8. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001; 111: 607-13.
9. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. J Clin Epidemiol 1998; 51: 415-22.
10. Pinola P, Piltonen TT, Puurunen J, Vanky E, Sundström-Poromaa I, Stener-Victorin E, et al. Androgen profile through life in women with polycystic ovary syndrome: a nordic multicenter collaboration study. J Clin Endocrinol Metab 2015; 100: 3400-7.
11. Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. Am J Clin Nutr 2006; 84: 77-87.
12. Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online 2006; 12: 569-78.
13. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2019; 3: CD007506.
14. Stahl JM, Malhotra S. Obesity Surgery Indications and Contraindications. 2023 Jul 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://pubmed.ncbi.nlm.nih.gov/30020657/
15. Maciejewski ML, Arterburn DE. Cost-effectiveness of bariatric surgery. JAMA 2013; 310: 742-3.
16. National Center for Biotechnology Information. PubChem Compound Summary for CID 104850, Rimonabant. [Internet]. 2022 [cited 2022 Jan 25]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Rimonabant
17. National Center for Biotechnology Information. PubChem Compound Summary for CID 5210, Sibutramine. [Internet]. 2022 [cited 2022 Jan 25]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5210
18. Dunaif A. Drug Insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome—a reappraisal. Nat Clin Pract Endocrinol Metab 2008; 4: 272-83.
19. Jamilian M, Zadeh Modarres S, Amiri Siavashani M, Karimi M, Mafi A, Ostadmohammadi V, et al. The influences of chromium supplementation on glycemic control, markers of cardio-metabolic risk, and oxidative stress in infertile polycystic ovary syndrome women candidate for in vitro fertilization: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2018; 185: 48-55.
20. Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raee MJ, Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: A randomized double-blind placebo controlled clinical trial. Phyther Res 2018; 32: 276-83.
21. Amini L, Mojab F, Jahanfar S, Sepidarkish M, Raoofi Z, Maleki-Hajiagha A. Efficacy of Salvia officinalis extract on the prevention of insulin resistance in euglycemic patients with polycystic ovary syndrome: A double-blinded placebo-controlled clinical trial. Complement Ther Med 2020; 48: 102245.
22. Haidari F, Banaei-Jahromi N, Zakerkish M, Ahmadi K. The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial. Nutr J 2020; 19: 8.

23. Khorshidi M, Moini A, Alipoor E, Rezvan N, Gorgani-Firuzjaee S, Yaseri M, et al. The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. Phyther Res 2018; 32: 2282-9.
24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 350: g7647.
25. Saha S, Saha S. The role of dietary supplements on anthropometric indices and metabolism of Sumanta of glucose and lipid in polycystic ovarian syndrome: A systematic review and network-meta-analysis of glucose of randomized controlled studies. PROSPERO 2022; CRD42022301530.
26. Saha S. Comparative effectiveness of adjunct non-pharmacological interventions on maternal and neonatal outcomes in gestational diabetes mellitus patients: A systematic review and network meta-analysis protocol of randomized controlled trials. PLoS One 2022; 17: e0263336.
27. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; 5: 210.
28. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. Wiley 2019. https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604
29. Saha S. Death and invasive mechanical ventilation risk in hospitalized COVID-19 patients treated with anti-SARS-CoV-2 monoclonal antibodies and/or antiviral agents: A systematic review and network meta-analysis protocol. PLoS One 2022; 17: e0270196.
30. Saha S, Saha S. The effects of prenatal dietary supplements on blood glucose and lipid metabolism in gestational diabetes mellitus patients: A systematic review and network meta-analysis protocol of randomized controlled trials. PLoS One 2022; 17: e0267854.
31. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Cochrane Collab 2011. https://training.cochrane.org/handbook/archive/v5.1/
32. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
33. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006; 11: 193-206.
34. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012; 3: 98-110.
35. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003; 326: 472.
36. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005; 9: 1-134.
37. Donegan S, Williamson P, Gamble C, Tudur-Smith C. Indirect comparisons: a review of reporting and methodological quality. PLoS One 2010; 5: e11054.
38. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012; 3: 80-97.
39. Caldwell DM. An overview of conducting systematic reviews with network meta-analysis. Syst Rev 2014; 3: 109.
40. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Intern Emerg Med 2017; 12: 103-11.
41. White IR. Network Meta-analysis. Stata J Promot Commun Stat Stata 2015; 15: 951-85.
42. Perera R, Heneghan C. Interpreting meta-analysis in systematic reviews. Evid Based Med 2008; 13: 67-9.
43. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011; 64: 163-71.
44. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Res Synth Methods 2012; 3: 161-76.
45. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013; 8: e76654.
46. Winters SJ, Talbott E, Guzick DS, Zborowski J, McHugh KP. Serum testosterone levels decrease in middle age in women with the polycystic ovary syndrome. Fertil Steril 2000; 73: 724-9.
47. Menopause - NHS [Internet]. [cited 2022 Feb 18]. Available from: https://www.nhs.uk/conditions/menopause/
48. Papilloud A, Guillot de Suduiraut I, Zanoletti O, Grosse J, Sandi C. Peripubertal stress increases play fighting at adolescence and modulates nucleus accumbens CB1 receptor expression and mitochondrial function in the amygdala. Transl Psychiatry 2018; 8: 156.
49. World Health Organization. Adolescent health [Internet]. Helath Top. [cited 2022 Feb 18]. Available from: https://www.who.int/health-topics/adolescent-health#tab=tab_1
50. Saha S. Efficacy trials comparing dosages of vitamin D and calcium co-supplementation in gestational diabetes mellitus patients require a methodological revamp. J Turk Ger Gynecol Assoc 2022; 23: 120-1.
51. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, 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.
52. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490.
53. Cote MP, Lubowitz JH, Brand JC, Rossi MJ. Understanding Network Meta-analysis (NMA) conclusions requires scrutiny of methods and results: introduction to NMA and the geometry of evidence. Arthroscopy 2021; 37: 2013-6.

Supplement Link 1: http://glns.co/oj7vl

Supplement Link 2: http://glns.co/yg6bx

Supplement Link 3: http://glns.co/89wuj