INPLASY PROTOCOL

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Conflicts of interest:
None.

Effects of inositol and alpha lipoic acid combination for polycystic ovary syndrome: a protocol for systematic review and meta-analysis

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Review question / Objective: **The objective of the present meta-analysis will be to evaluate the efficacy and safety of inositol and alpha lipoic acid combination in adult women with a diagnosis of PCOS.**
Condition being studied: **Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It is characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovaries. Although the exact etiology of PCOS remains unclear, insulin resistance and oxidative stress play a pivotal role in the pathophysiology of PCOS. Recently several small studies have indicated that inositol and alpha lipoic acid supplementation can ameliorate certain outcomes in PCOS women. However, there is a lack of sufficient evidence to affirm this practice.Therefore, we will conduct a systematic review to evaluate the effectiveness and safety of inositol and alpha-lipoic acid combination, with a focus on clinical, metabolic and endocrine dysfunctions in women suffering from PCOS.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 May 2020 and was last updated on 03 May 2020 (registration number INPLASY202050011).

INTRODUCTION

Review question / Objective: **The objective of the present meta-analysis will be to evaluate the efficacy and safety of inositol and alpha lipoic acid combination in adult women with a diagnosis of PCOS.**

Rationale: **Currently, there is no systematic review focusing on the effectiveness and safety of inositol and alpha lipoic acid combination therapy for women with PCOS, so our meta-analysis aims to comprehensively explore it. Meanwhile we will provide high-quality evidence to help patients, clinicians as well as health policymakers select better treatment strategy of PCOS.**

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METHODS

Search strategy: We will search the following electronic databases: PubMed, EMBASE, The Web of Science, The Cochrane Library of Controlled Trials, Clinical Trials. gov, Chinese Biomedical Literature Database (CMB), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wan-Fang database without limitations on language. We will also hand-search reference lists and grey literature to acquire additional studies. A search strategy that combines MeSH terms and free words will be adopted by us. Search terms will be as follows: polycystic ovary syndrome (PCOS), inositol, myo-inositol (MI), D-chiro-inositol (DCI), alpha-lipoic acid (ALA), randomized controlled trials etc.

Participant or population: Adult women with a diagnosis of polycystic ovary syndrome according to Rotterdam Criteria 2003, National Institute of Health (NIH) Criteria 1990, or Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society Criteria. Adolescents (under 18 years old) and post-menopausal women (over 50 years old) will be excluded from the review.

Intervention: Intervention strategies are composed of myo-inositol (MI)/D-chiro-inositol (DCI) and alpha lipoic acid combination, with any dosage, frequency and duration.

Comparator: The control can include blanks, placebo, any active treatment or lifestyle interventions such as diet and exercise.

Study designs to be included: Only human (women) studies and randomized clinical trials will be included.

Eligibility criteria: Inclusion criteria: (1) Women with a diagnosis of polycystic ovary syndrome; (2) The interventional therapy is myo-inositol (MI)/D-chiro-inositol (DCI) and alpha lipoic acid combination; (3) The control therapies include blanks, placebo, and/or Western medicine; (4) Randomized controlled trials will be included, with no limitations imposed on the method of randomization or blinding used, or on the language of publication. Exclusion criteria: (1) Adolescents (under 18 years old) and post-menopausal women (over 50 years old); (2) Other aetiologies of menstrual disturbance and hyperandrogenism such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome.

Information sources: We will search the following electronic databases: PubMed, EMBASE, The Web of Science, The Cochrane Library of Controlled Trials, Clinical Trials. gov, Chinese Biomedical Literature Database (CMB), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wan-Fang database without limitations on language. We will also hand-search reference lists and grey literature to acquire additional studies. We will contact the first author or correspondent author of relevant studies to obtain the sufficient information via email or telephone.

Main outcome(s): Primary outcomes consist of menstrual cycle regulation, body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-

IR). Different evaluation methods are selected according to the different efficacy indicators. For each dichotomous outcome, we will choose relative risk (RR). While each continuous outcome is expressed as mean difference (MD). We will present 95% confidence intervals (CI) for all outcomes.

Additional outcome(s): (1) Clinical outcomes: Ferriman-Gallway score, waist to hip ratio (WHR), systolic and diastolic blood pressure. (2) Metabolic outcomes: blood glucose and insulin parameters, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). (3) Endocrine outcomes: leutinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estradiol (E2), progesterone, serum sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS). (4) Any adverse event.

Data management: Two methodological trained researchers will separately select the pertinent literature. Retrieved literature will be imported into the software of Endnote X9 and duplicate literature will be deleted. Then we will extract data into Microsoft Excel spreadsheet.

Quality assessment / Risk of bias analysis: Two independent reviewers will evaluate the methodological quality of individual studies employing the Cochrane risk of bias assessment tool. The following domains are affiliated with bias risk, including randomized method, allocation concealment, blinding of participants and staff, blinding of outcome assessment, completeness of outcome data, selective reporting and other biases. Each entry will be allocated a RoB rating of low, high or unclear risk. Diverse opinions between both reviewers will get a consensus or arbitration with a third one as required.

Strategy of data synthesis: We will perform data synthesis using the software of Review Manager version 5.3 offered by the Cochrane Collaboration. The data will be merged as MD or RR with 95% confidence intervals for continuous variables or the categorical. Homogeneous data will be pooled through a fixed effect model. Inversely, a random effect model will be applied.

Subgroup analysis: To identify explanations of heterogeneity between adequate studies (>10) and answer questions of clinical interest, we will conduct subgroup analyses within the following aspects, type of inositol, family history of diabetes mellitus and insulin resistance.

Sensibility analysis: We will assess the robustness and reliability of the meta-analysis results by a sensitivity analysis for the primary outcomes. We will eliminate each of the eligible studies one by one, and then merge the data and re-analyze. Subsequently, the distinction between the regenerated effects and the original effects will be compared. We will determine the impact on the conclusions of meta-analysis, such as risk of bias, effect sizes, statistical models.

Language: There are no restrictions imposed on the language of publication.

Country(ies) involved: China.

Keywords: inositol; alpha lipoic acid; polycystic ovary syndrome; protocol; systematic review and meta-analysis.

Dissemination plans: We will publish the final results of our study in a peer-reviewed journal.

Contributions of each author:
Author 1 - Wenwen Lei - The author drafted and revised the manuscript.
Author 2 - Yang Gao - The author provided statistical expertise.
Author 3 - Shiruo Hu - The author will extract data, assess the risk of bias and conduct data synthesis.
Author 4 - Dongyin Liu - The author will extract data, assess the risk of bias and conduct data synthesis.
Author 5 - Qiu Chen - The author read, provided feedback and approved the final manuscript.