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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202390021

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 September 2023 and was last updated on 07 September 2023.

INTRODUCTION

Review question / Objective What is the association between plasma homocysteine levels and pregnancy outcomes among women with polycystic ovary syndrome (PCOS). The selected research method is Meta-Analysis.

Condition being studied Polycystic ovary syndrome (PCOS) is a complex disease that involves the cardiovascular, metabolic, endocrine, and reproductive systems. Although the exact cause is not yet clear, many studies have shown that genetic and environmental factors play a role. High homocysteine (HHCY) is closely related to the occurrence and development of many diseases, such as cardiovascular and cerebrovascular diseases, hypertension, diabetes, kidney diseases, pregnancy and other diseases, affecting almost all organs of the body. The negative effects of HHCY

on reproductive processes have been documented in numerous studies, including poor oocyte quality, male infertility caused by abnormal sperm morphology, low sperm counts and loss of motility, congenital malformation, miscarriage, hypertension and low birth weight. In recent years, clinical attention to homocysteine has been increasing, and studies have shown an important correlation between elevated homocysteine (HCY) concentration and PCOS. To date, research surrounding the exact effect of plasma homocysteine levels on polycystic ovary syndrome patients' pregnancy outcomes remains limited. The purpose of this study was to determine the association and contribution of high HCY and metabolic syndrome on ovulation, conception, pregnancy, pregnancy loss and live birth in infertile women with PCOS. We aimed to determine whether higher HCY levels are predictive of a rapid

decline in ovulation function and an increase in pregnancy loss among women with PCOS.

METHODS

Search strategy PubMed, Medline, Embase and all databases of the Cochrane library were searched from 1 January 2000 to 1 September 2023 in English language. The primary search strategy was as follow: ('polycystic ovary syndrome' OR 'PCOS' OR 'Stein-Leventhal' OR 'hyperandrogenism' OR 'sclerocystic ovaries' OR 'polycystic ovaries') AND ('homocysteine' OR '2-amino-4-mercaptobutyric acid') AND ('pregnancy-related outcomes' OR 'pregnancy' OR 'reproduction'). A manual search was conducted on the references of the retrieved articles. In order to select the research to be included in the analysis, we first reviewed the article title and abstract, and then obtained the full text to verify its eligibility.

Participant or population Women with polycystic ovary syndrome.

Intervention Plasma homocysteine levels.

Comparator Normal plasma homocysteine.

Study designs to be included Research using cross-sectional studies, case-control studies, or cohort design.

Eligibility criteria The inclusion criteria include: (1) a study comparing reproductive related indicators between women of childbearing age with high plasma homocysteine PCOS and those with normal plasma homocysteine PCOS; (2) Using the Rotterdam PCOS standard. Exclusion criteria include: (1) Studies reporting less than 10 cases and/or controls, (2) comments, case reports, conference abstracts/articles, editorials, letters, (3) unrelated to the research question, (4) studies did not show plasma homocysteine concentrations in the control group, or did not show plasma homocysteine concentrations in the control group and patients, (5) homocysteine measurements in follicular fluid, (6) did not respond to requests for data clarification. (7) The same author has a larger series of cases.

Information sources PubMed, Medline, Embase and all databases of the Cochrane library were searched from 1 January 2000 to 1 September 2023 in English language. A manual search was conducted on the references of the retrieved articles. In order to select the research to be included in the analysis, we first reviewed the

article title and abstract, and then obtained the full text to verify its eligibility.

Main outcome(s) pregnancy rate; ovulation rate; pregnancy loss rate; live birth rate.

Additional outcome(s) Incidence of adverse reactions.

Data management Data extraction from each study was performed by two authors independently. Patients' basic characteristics, plasma homocysteine levels, results of laboratory tests, pregnancy rate, ovulation rate, pregnancy loss rate, live birth rate, incidence of adverse reactions were exacted from each study using a predesigned data extraction form. For the missing information, we tried to contact the authors of original articles. During the process of data extraction, any disagreement was resolved by discussion.

Quality assessment / Risk of bias analysis The study quality assessment /risk of bias analysis was conducted by two reviewers independently. The Newcastle-Ottawa Scale (NOS) was performed to evaluate the quality of observational study, and adapted NOS for cross-sectional studies (NOS-CS). The risk of bias is divided into low bias risk (≥ 7 stars) or high bias risk (≤ 6 stars). During the process of quality assessment, any disagreement was resolved by discussion.

Strategy of data synthesis Dichotomous variables were tested by Risk Ratio (RR) with a 95% confidence interval (CI), and continuous variables were tested by the standardized mean difference (SMD) with a 95%CI. Random effect model was used for all calculations. Heterogeneity between studies was tested by chi-squared test (with significance set at $p > 0.1$) and I-squared test. Funnel plots were also used to investigate the publication bias if sufficient studies existed. A value of $p < 0.05$ was considered statistically significant.

Subgroup analysis If there is substantial heterogeneity between studies, then subgroup analysis will be conducted to investigate the sources of heterogeneity.

Sensitivity analysis We will omit each study that is included in meta-analysis one by one if there are sufficient studies.

Language restriction English.

Country(ies) involved China.

Keywords Homocysteine; Polycystic Ovary Syndrome; Pregnancy Outcome; Meta-analysis.

Contributions of each author

Author 1 - Nianjun Su - Study Design, Data collection and analysis, Result discussion, Manuscript writing, Proof reading and editing.

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