INPLASY

Comparison of combined clomiphene and letrozole versus only letrozole for ovulation induction in women with polycystic ovarian syndrome: a systematic review and meta-analysis

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Feng, J[1]; Duan, S[2]; Ahemd, W[3].

Corresponding author:
Jia Feng

1635094571@qq.com

Author Affiliation:
Guangdong Second Provincial General Hospital.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 August 2023 and was last updated on 25 August 2023.

INTRODUCTION

Review question / Objective To evaluate the efficacy of combination treatment of letrozole and clomiphene citrate (CC) in comparison to that of letrozole alone to induce ovulation in infertile women with polycystic ovary syndrome (PCOS).

Condition being studied Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women and the most common cause of anovulatory infertility. The treatment of infertility in patients with PCOS focuses on ovulation induction. Many treatment regimens have been used, with varying success, to achieve ovulation, pregnancy, and live birth. Clomiphene citrate (CC) is a commonly prescribed pharmacologic agent used to induce ovulation in women with PCOS.It works as a selective estrogen receptor modulator by competitively attaching to nuclear estrogen receptors. As the negative feedback of estrogen is reduced, secretion of gonadotropin hormones increases, inducing ovarian follicular growth. CC alsohas an antiestrogenic effect on endometrial development and cervical mucus production, which has been suggested to contribute to a relatively low pregnancy rate despite a high ovulation rate. Letrozole is another commonly used oral ovulation induction agent, with a different mechanism of action. It works as a highly selective aromatase inhibitor, preventing androgen-to-estrogen conversion. One proposed mechanism is via suppressed estrogen production resulting in decreased negative feedback on the hypothalamus and increased secretion of FSH. An additional proposed mechanism of improved ovulatory rates with the use of letrozole is increased follicular sensitivity to FSH resulting from temporarily increased intraovarian androgens. Letrozole may offer a benefit over CC for ovulation induction because it does not block estrogen receptors in both central and peripheral target tissues, and normal central feedback mechanisms remain intact. The Pregnancy and Polycystic Ovary Syndrome (PPCOS) II trial, a randomized controlled trial comparing letrozole and CC, demonstrated

that letrozole was associated with a higher live birth rate (27.5% vs. 19.1%; P¼.007; rate ratio 1.44, 95% confidence interval [CI] 1.10–1.87) and cumulative ovulation rate (61.7% vs. 48.3%; P<.001) among women with PCOS. Other than letrozole or CC for ovulation induction, there are few treatment options available to PCOS patients except proceeding to gonadotropin injections or in vitro fertilization, both of which are associated with increased cost and risk. Because letrozole and CC have different mechanisms of action, we postulated that the combination of these medications may result in an improved ovulatory rate over letrozole alone. Since there have been no previous systematic reviews and meta-analyses comparing clomiphene combined with letrozole versus letrozole alone in ovulation promotion in women with PCOS, we hope to conduct a systematic review. .If the combination results in a higher ovulatory rate, larger studies evaluating the pregnancy and delivery rates with the combined therapy would be indicated. Therefore, our aim was to test the hypothesis that combined therapy of letrozole and CC is effective and superior to the use of letrozole alone to achieve ovulation in women with PCOS.

METHODS

Participant or population Women with Polycystic ovary syndrome (PCOS).

Intervention Combined clomiphene and letrozole.

Comparator Letrozole only.

Study designs to be included RCTs.

Eligibility criteria All abstracts and titles were screened by three independent authors to select eligible clinical articles. We included studies that met the following inclusion criteria: (1) RCT (2) combined clomiphene and letrozole versus only letrozole for ovulation induction in women with polycystic ovarian syndrome; (3) Outcome reported and (4) The number of patients per group were stated within the publication. We also excluded non-RCTs, literature reviews, meta-analysis, meeting abstracts, case reports, repeated studies, experimental model researches, and other diseases researches.

Information sources Pubmed, Embase, CNKI.

Main outcome(s) Ovulation, conception, clinical pregnancy, live birth, pregnancy loss, and so on.

Quality assessment / Risk of bias analysis The quality of each study was assessed independently by the same two investigators using the Risk of Bias Tool developed by the Cochrane Collaboration. For each RCT, the investigators freely scored low risk, high risk, and unclear risk according to the following rules: sequence generation; allocation concealment; blinding of participants and personnel, and blinding of outcome assessment; incomplete outcome data; selective reporting; and other potential sources of bias. Funnel plot and Egger's test were used to detect publication bias; no publication bias was identified with a $p<0.05$.

Strategy of data synthesis All analyses were performed using STATA 15.0 and Review Manager (RevMan version 5.3) software and dichotomous data from published studies were used to generate risk ratios (RRs) with 95% confidence intervals (CIs), and a meta-analysis was performed with a Mantel–Haenszel fixed-effects model to calculate a summary RR with 95% CIs. $P\leq0.05$ means there is a statistical significance. Spearman correlation analysis was used to test heterogeneity caused by threshold effect; if I^2 >75% and $p>0.05$, a meta-regression analysis was used to find the sources of heterogeneity.

Subgroup analysis No.

Sensitivity analysis No.

Country(ies) involved China.

Keywords clomiphene, letrozole, polycystic ovarian syndrome.

Contributions of each author
Author 1 - Jia Feng.
Author 2 - Shan Duan.
Author 3 - Ahmed Waqas.