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Review

Systematic review and meta-analysis of letrozole and clomiphene citrate in polycystic ovary syndrome

Abdul Qadr Akinoso-Imran [a,*], Hamed Adetunji [b]

[a] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[b] Faculty of Public Health and Health Informatics, Department of Epidemiology, Umm Al-Qura University, Makkah, Saudi Arabia

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ABSTRACT

This study aims to systematically evaluate the clinical efficacy and safety of both clomiphene citrate (CC) and letrozole, and to examine if the efficacy of letrozole is superior to CC in women with polycystic ovary syndrome (PCOS).

Major databases were searched for eligible randomised controlled trials (RCTs). The methodological quality of the included studies was assessed by two independent reviewers. Meta-analysis was performed using random-effect model to account for the high levels of heterogeneity. Overall, ten eligible RCTs involving 1905 women were included. Letrozole was associated with significantly higher ovulation rate (relative risk (RR) 1.20; 95% CI 1.03–1.40; P = 0.02); clinical pregnancy rate (RR 1.48; 95% CI 1.12–1.94; P = 0.005) and endometrial thickness (standardized mean difference (SMD) 2.31; 95% CI 0.85–3.76; P = 0.002). There was no evidence of a difference between the treatment groups in the rate of miscarriage, number of mature follicles and multiple pregnancy rates. The result suggests that letrozole is a superior ovulation induction agent for women with PCOS as it is associated with higher ovulation and clinical pregnancy rates with no obvious increased side effects. However, this conclusion should be considered with a slight caution in that the quality of the evidence could have improved if more recent studies on the subject were available to be included in the review.

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* Corresponding author.
E-mail addresses: abdqad87@gmail.com (A.Q. Akinoso-Imran), haadetunji@uqu.edu.sa (H. Adetunji).
@AbdulQadrImran (A.Q. Akinoso-Imran)

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1. Introduction

Polycystic ovary syndrome (PCOS) is undisputedly the most common gynecological endocrinopathy [1]. Although PCOS is underdiagnosed [2], its prevalence ranges between 2.2% and 26% in different countries [3], and 6.8–18% in women of reproductive age [4], using different diagnostic criteria and recruitment method of the study population.

The primary clinical indicator of PCOS is irregular or lack of menstrual cycles and infertility. There is a clear link between PCOS and infertility, as PCOS is responsible for 55% to 70% of infertility cases resulting from chronic anovulation, thus, it is among the most common causes of infertility due to ovulation dysfunction [4]. Although, around 60% of those with PCOS are considered fertile [5].

Ovulation induction is a standard treatment procedure many PCOS patients experience. Clomiphene citrate (CC) is typically considered the first choice drug treatment for ovarian stimulation [6,7]. About 80% of women with PCOS respond to treatment with clomiphene (i.e. ovulate) and half of them will become pregnant [8]. While CC is highly effective in selected patients, it is associated with certain undesired effects including inconsistency concerning ovulation and conception rates, high rate of miscarriage [9,10], long clearance half-life of around 5 days to 3 weeks (depending on the isomer) [11], which is 'anti-oestrogenic' and thus, may negatively affect the endometrium and cervical mucus by preventing pregnancy [11,12].

As an alternative, aromatase inhibitors (Als) were introduced in 2001 for ovulation induction by Mitwally and Casper 2001 [13]. Letrozole is the most commonly used Al to induce ovulation. It is formally manufactured to prevent and treat hormone-responsive breast cancer, however, since 2001 doctors have been prescribing it to women that fail to respond to CC and has appeared to avoid the unfavourable effects of CC. Since its introduction, many studies have confirmed letrozole's effectiveness in ovulation stimulation and from many clinical trials have suggested that letrozole might be as effective as CC, although figures vary [14]. In addition, several studies have indicated that interventions based on letrozole are likely to elude the adverse effects associated with CC such as shorter half-life, an increased frequency of monofollicular ovulation [15] and the absence of antiestrogenic effects on the endometrium [16].

Recently, several randomised controlled trials (RCTs) have been conducted to assess the efficiency and safety of letrozole in PCOS [16,17], nevertheless conclusions have not been very decisive. Moreover, there has only been few meta-analysis to provide evidence to show whether letrozole is superior to CC, again with no definite conclusion. As such, this systematic review and meta-analysis is designed to evaluate the clinical efficacy and safety of both CC and letrozole and to especially fill the research gap examining whether or not the efficacy of letrozole is superior to CC.

2. Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [18].

2.1. Search strategy

To obtain relevant studies without language restriction, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) [inception to 9 March 2015], MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) [inception to 9 March 2015], EMBASE [inception to 9 March 2015] and PsycINFO [inception to 9 March 2015]. Other resources such as PubMed, clinicaltrials.gov, WHO's database, web of knowledge, and Google Scholar were also searched. The following keywords were used to search for relevant articles: letrozole, aromatase inhibitors, clomiphene citrate, polycystic ovary syndrome, hyperandrogenism, anovulation, ovulation induction and randomized controlled trial.

2.2. Eligibility criteria

After conducting the initial search, the retrieved articles were screened for eligibility using the following inclusion criteria: (1) an RCT; (2) women diagnosed with PCOS according to the Rotherdam criteria, by two of the following three features: oligoovulation (infrequent ovulation) and/or anovulation (absence of ovulation), hyperandrogenism (diagnosed clinically or biochemically) and the presence of polycystic ovaries; (3) lectrozole against CC for ovulation induction (alone or combined with metformin) followed by any possible method of reproduction (e.g. timed sexual intercourse, Intrauterine insemination (IUI) and In vitro fertilisation (IVF); (4) the outcome included at least one of the following: ovulation rate per cycle, clinical pregnancy rate per woman randomized, miscarriage rate per woman randomized, number of mature follicles, endometrial thickness at human chorionic gonadotrophin (HCG), multiple pregnancy rates per women randomized, multiple pregnancy rate and Serum E_2 concentration.

2.3. Study selection and assessment

Individual search results were combined and filtered for only RCTs. Studies from any country were included, even though English language was necessary for inclusion. Titles and abstracts were screened independently by the two reviewers against the eligibility criteria mentioned above. Full papers of abstracts that appear to meet the inclusion criteria were retrieved and thoroughly screened. Studies with other cause of infertility or that presented inadequate methodology and results were excluded.

In line with the Cochrane risk of bias tool [19], the reviewers assessed the included studies for seven areas of potential biases i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and Other bias.

Each study was assessed regarding these potential areas of biases and categorized as either, "high risk", "low risk" or "unclear risk", using the criteria from the Cochrane assessment tool [19].

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