Letrozole vs clomiphene citrate in the management of infertility in women with polycystic ovary syndrome

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Abstract

Background: Poly cystic ovary syndrome (PCOS) is the most common endocrine disorder leading to anovulatory infertility. Both clomiphene citrate and letrozole are widely used for ovulation induction, but their relative effectiveness remains a subject of debate.

In this literature review we critically analyze randomized controlled trials comparing letrozole to clomiphene citrate in respect to:

- main outcome: ovulation rate, pregnancy rate and pregnancy outcome
- secondary outcome: miscarriage rate, endometrial thickness, multiple pregnancy and side effects of the medications

Methodology: A review of published articles was conducted including systematic review and meta-analysis, double blind randomized controlled trails focusing on data from the last 5 years, with the focus of the study on ovulation rate, pregnancy rate and outcome (live birth rates), with some secondary outcomes such as miscarriage rate and endometrial thickness.

Results: Letrozole showed better outcome than clomiphene citrate in terms of mean endometrial thickness, ovulation rate and pregnancy rate and outcomes with better side effect profile observed in some trials.

Key words:
Polycystic ovary syndrome (PCOS), letrozole, clomiphene citrate

Introduction

The polycystic ovary syndrome (PCOS) is an important cause of both menstrual irregularity and androgen excess in women. PCOS can be readily diagnosed when women present with the classic features of hirsutism, irregular menstrual cycles, and polycystic ovarian morphology on transvaginal ultrasound (TVUS). However, there has been considerable controversy about specific diagnostic criteria when not all of these classic features are evident.

Estimated prevalence of PCOS varies from 6.3% using 2023 International guideline adolescent diagnostic criteria to 9.8% using original Rotterdam PCOS diagnostic criteria in female persons aged 10-19 years (systematic review). The syndrome is characterized clinically by oligomenorrhea and hyperandrogenism, as well as the frequent presence of associated risk factors for cardiovascular disease, including obesity, glucose intolerance, dyslipidemia, fatty liver and obstructive sleep apnea.

The etiology of PCOS is unclear, although it is thought to emerge from a combination of genetic and epigenetic factors, hypothalamic and ovarian dysfunction, excess exposure to androgen, insulin resistance and mechanisms related to excess adiposity.

PCOS is frequently diagnosed in women presenting with infertility issues.

The main management options are:
- management of patient who is not seeking infertility (includes acne, hirsutism, female pattern hair loss and management of menstrual irregularities)
- management of patients who seek fertility (which includes lifestyle modifications and medications)

Letrozole is an aromatase inhibitor and can be used as an oral ovulation induction agent; aromatase inhibitors prevent estrogen biosynthesis from androgens by inhibiting aromatase conversion of androgens to estrogens, including in the ovary.

The decline in estrogen levels leads to an increase in follicle-stimulating hormone through hypothalamic/pituitary feedback, resulting in stimulation of ovarian follicle development and maturation.

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that blocks estradiol receptors in the hypothalamus and induces changes in gonadotropin releasing hormone pulse frequency, leading to release of follicle-stimulating hormone from the anterior pituitary and stimulation of follicular development.

While clomiphene citrate has traditionally been used as first-line therapy for management of anovulatory infertility, letrozole may now be preferred due to the following advantages:

- letrozole preserves ovarian/pituitary feedback (in contrast to clomiphene citrate), which reportedly reduces the risk of multiple follicle development compared to clomiphene citrate
- letrozole does not affect endometrial estrogen receptors (in contrast to clomiphene citrate), and therefore, does not adversely impact endometrial thickness or cervical mucus
- half-life is 2 days for letrozole compared to 5 days for clomiphene citrate

Many studies recommend the use of letrozole as first line for infertility in patients with PCOS with recommendations from: American College of Obstetricians and Gynecologists (ACOG) recommends letrozole as first-line ovulation induction therapy over clomiphene citrate due to increased live birth rate with letrozole compared with clomiphene citrate (ACOG Level A); Use letrozole as the preferred first-line treatment to induce ovulation in patients with anovulatory infertility and no other fertility factors (International PCOS Network Strong recommendation for the option, High-quality evidence).

Methodology

The literature sources used were PubMed, Cochrane, and Google Scholar. We choose literature published within the last 5 years, namely from 2019-2024. After that, a selection of journals with open access criteria was carried out and literature that met the criteria was obtained in 10 journals.

Studies included were RCTs of infertile women with PCOS (Rotterdam 2003 criteria) comparing clomiphene citrate and letrozole.

Interventions involved timed intercourse or intrauterine insemination.

At least one primary or secondary outcome had to be reported.

Excluded studies were non-clinical, observational, reviews, or animal/cell studies, or involved drug resistance or other infertility causes.

Articles with incomplete data, mixed interventions, irrelevant outcomes, or not in English were also excluded.

Main outcomes: ovulation rate per cycle, clinical pregnancy rate, and live-birth rate.

Secondary outcomes: miscarriage rate per patient and per pregnancy, multiple pregnancy rate per patient and per pregnancy.

Endometrial thickness at midcycle measured by ultrasound was also recorded.

Results and Discussion

The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on ovulation rates

The majority of the included studies reported higher ovulation rates with letrozole when compared to clomiphene citrate.

A systematic review and metanalysis, indicated that letrozole increased the ovulation rate per cycle in patients with PCOS compared with clomiphene citrate (RR 1.14, 95% CI 1.06–1.21, P<.001).

The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on Pregnancy Rate and outcome

Overall, available evidence suggests that letrozole may result in higher pregnancy rates and better reproductive outcome (live birth) than clomiphene citrate in patient with PCOS.

Reviewing the latest systematic review letrozole was more effective in promoting pregnancy than clomiphene citrate (34.6% vs 23.4%, RR 1.48, 95% CI 1.34–1.63, P<.001) and higher live births (32.8% vs 22.2%, RR 1.49, 95% CI 1.27–1.74, P<.001).

Some secondary outcomes

Some studies also highlighted secondary outcomes such as endometrial thickness. It indicated that letrozole was associated with improving endometrial thickness compared with clomiphene citrate (9.02 mm vs 7.55 mm, mean difference 1.50, 95% CI 0.96–2.04, P<.001).

Rates of miscarriage were similar between the two treatment groups; however, treatment with letrozole was associated with fewer multiple pregnancies compared with clomiphene citrate.

At the time of this review, there is a lack of sufficient evidence to fully assess differences in adverse effects between the letrozole group and the clomiphene citrate group.

Conclusion

Based on this literature review, it was found that Letrozole is superior to Clomiphene Citrate (CC) as an ovulation induction agent in PCOS patients. Letrozole is also associated with a better probability of pregnancy and live birth.

The probability of miscarriage and the occurrence of congenital anomalies or defects in the newborn did not differ between the groups receiving letrozole and those with CC.

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