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Original Research Article

A comparative study of letrozole and clomiphene citrate for ovulation induction in women with polycystic ovarian syndrome: a randomized controlled trial

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ABSTRACT

Background: Effective ovulation induction is crucial in management of polycystic ovarian syndrome (PCOS) related infertility. Clomiphene citrate (CC) has long been the first line of treatment for inducing ovulation in women with PCOS. Letrozole, an aromatase inhibitor, has emerged as a promising alternative to CC for ovulation induction. The present study was aimed to compare efficacy and safety of letrozole versus CC for ovulation induction in women with PCOS.
Methods: This study consists of 384 PCOS women, randomized into two groups: Letrozole (2.5 mg/day) and CC (50 mg/day), both administered from day 3 to day 7 of the menstrual cycle. The primary outcome was the ovulation rate, confirmed by serum progesterone levels >10 ng/ml. Secondary outcomes included clinical pregnancy rate, live birth rate, endometrial thickness, adverse effects, cost-effectiveness, and patient satisfaction. Participants were monitored through transvaginal ultrasound and serum progesterone measurements.
Results: Ovulation was achieved in 76.0% of participants in the letrozole group compared to 55.2% in the CC group ($p<0.001$). Clinical pregnancy rates were significantly higher in the letrozole group (44.8%) compared to the CC group (28.1%) ($p<0.001$). Similarly, live birth rates were higher with letrozole (36.5% vs. 22.4%; $p=0.002$). Endometrial thickness was greater in the letrozole group (8.7 mm vs. 7.5 mm; $p<0.001$). Adverse effects, were significantly lower in the letrozole group.
Conclusions: Letrozole is more effective than CC in inducing ovulation and achieving higher pregnancy and live birth rates in women with PCOS.

Keywords: Polycystic ovary syndrome, Letrozole, CC, Ovulation induction, Infertility

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries.[1] It affects approximately 6-15% of women globally, making it a significant concern for female fertility. One of the primary challenges for women with PCOS is anovulation, which leads to infertility.[2] Effective ovulation induction is therefore crucial in management of PCOS-related infertility. CC has long been first-line treatment for inducing ovulation in women with PCOS due to its ability to increase gonadotropin release by blocking estrogen receptors in the hypothalamus.[3] However, up to 20-25% of women with PCOS are resistant to CC, failing to ovulate with standard treatment regimens. This resistance necessitates alternative therapies that can effectively induce ovulation in CC-resistant women. Letrozole, an aromatase inhibitor, has emerged as promising alternative to CC for ovulation induction.[4] By inhibiting conversion of androgens to estrogens, letrozole reduces estrogen

feedback on the hypothalamus, leading to increased FSH secretion and subsequent follicular development. Several studies have suggested that letrozole may be superior to CC in terms of ovulation and live birth rates, particularly in women with PCOS.[3,4]

Despite the growing body of evidence supporting the use of letrozole, there is still a need for comprehensive, randomized controlled trials (RCT) to definitively compare its efficacy and safety with CC. This study aims to address this gap by evaluating the ovulation rates, pregnancy outcomes, and side effect profiles of letrozole versus CC in women with PCOS. By utilizing serum progesterone levels as a biochemical marker of ovulation, this study seeks to provide robust data on the comparative effectiveness of these two ovulation induction agents.

METHODS

Study design

This is a RCT designed to compare the efficacy and safety of letrozole and CC for ovulation induction in women with PCOS. Participants were randomly assigned to either the letrozole group or the CC group in a 1:1 ratio. The study was conducted for 12-month period at a tertiary care fertility center, Sri Venkateshwara Medicity Hospital, Tamil Nadu during the period of March 2023 to May 2024.

Participants

Study included women aged 18-40 years, diagnosed with PCOS based on the Rotterdam criteria, which require two out of 3 of following: oligo-or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound. Exclusion criteria include other causes of infertility (e.g., tubal factor, severe male factor), previous ovarian surgery, untreated thyroid or adrenal disorders, and hypersensitivity to either study medication.

Randomization and blinding

Participants were randomized using a computer-generated randomization sequence.

Allocation

Concealment was ensured using sealed, opaque envelopes. Due to the nature of the medications and their administration, the study was open-label, meaning both participants and healthcare providers were aware of the treatment allocation. However, outcome assessors were blinded to the group assignments to minimize bias.

Interventions

Letrozole group: Participants in this group received letrozole 2.5 mg orally once daily from day 3 to day 7 of the menstrual cycle.

CC group: Participants in this group received CC 50 mg orally once daily from day 3 to day 7 of the menstrual cycle.

The dosage of both medications may be increased in subsequent cycles if ovulation is not achieved, up to a maximum of 7.5 mg/day for letrozole and 150 mg/day for CC.

Monitoring and follow-up

Participants were monitored through transvaginal ultrasounds starting on day 10 of the menstrual cycle to assess follicular development. Ultrasound monitoring was continued, every 2-3 days until the leading follicle reaches a mean diameter of ≥18 mm. At this point, an injection of 5,000 to 10,000 IU of human chorionic gonadotropin (hCG) was administered to trigger ovulation.

Seven days after hCG injection, serum progesterone levels were measured to confirm ovulation. Progesterone levels >10 ng/ml will be considered indicative of ovulation. Participants asked to have timed intercourse/intrauterine insemination (IUI) as appropriate.[5,6]

Primary outcome

The primary outcome was the ovulation rate, defined by serum progesterone levels >10 ng/ml seven days post-hCG trigger.

Secondary outcomes

Clinical pregnancy rate, confirmed by the presence of a gestational sac with a heartbeat on ultrasound at 6-8 weeks of gestation. Live birth rate, defined as the delivery of a viable infant after 24 weeks of gestation. Incidence of multiple pregnancies. Endometrial thickness measured at the time of hCG administration. Incidence and severity of adverse effects (e.g., hot flashes, mood swings, visual disturbances).[7] Duration of treatment cycles until ovulation is achieved. Cost-effectiveness of each treatment, including medication costs and healthcare resource utilization. Patient satisfaction and preference, assessed through standardized questionnaires.

Data collection

Data was collected at each clinic visit and entered into a secure, password-protected database. Baseline data include demographic information, medical and reproductive history, and baseline hormone levels. Follow-up data include ultrasound findings, serum progesterone levels, pregnancy outcomes, and any adverse events reported.

Sample size calculation

Based on previous studies, an ovulation rate difference of 10% between letrozole and CC is considered clinically

significant. With an alpha level of 0.05 and a power of 80%, a sample size of 160 participants per group (320 total) is required. To account for a 20% dropout rate, the final sample size will be adjusted to 384 participants (192 per group).

Ethical considerations

The study protocol is reviewed and approved by the institutional review board (IRB) or ethics committee. Informed consent is obtained from all participants prior to enrolment. Participant confidentiality is maintained throughout the study, and data is anonymized for analysis.

Statistical analysis

Statistical analysis was performed using SPSS software. Descriptive statistics used to summarize baseline characteristics and outcomes. Continuous variables were compared using the independent t test or Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. The primary analysis was intention-to-treat, including all randomized participants. A per-protocol analysis was also conducted to assess the impact of protocol adherence on outcomes. Kaplan-Meier survival analysis is used to compare time-to-ovulation and time-to-pregnancy between the two groups.

RESULTS

The study enrolled a total of 384 women diagnosed with PCOS, with 192 participants randomized to the letrozole group and 192 to the CC group. The baseline characteristics of the participants were comparable between the two groups (Table 1).

Table 1: Baseline characteristics of study participants.

Characteristic	Letrozole group, (n=192)	CC group, (n=192)	P value
Age (in years)	28.4±4.1	28.6±4.3	0.67
BMI (kg/m²)	27.2±5.4	26.9±5.1	0.54
Duration of infertility (years)	3.5±2.2	3.4±2.1	0.78
Baseline FSH (IU/l)	6.1±1.4	6.3±1.5	0.34
Baseline LH (IU/l)	8.7±3.2	8.5±3.1	0.62
Baseline testosterone (ng/dl)	55.3±17.8	54.9±18.1	0.84

Ovulation rates

The primary outcome of ovulation was achieved in a significantly higher proportion of participants in the letrozole group compared to the CC group (Table 2).

Table 2: Ovulation rates.

Outcome	Letrozole group, (n=192)	CC group, (n=192)	P value
Ovulation rate (%)	76.0 (146/192)	55.2 (106/192)	<0.001
Average serum progesterone (ng/ml)	13.2±4.1	11.4±3.8	<0.001

Pregnancy outcomes

Clinical pregnancy rate and live birth rate were also higher in letrozole group (Table 3).

Table 3: Pregnancy outcomes.

Outcome	Letrozole group, (n=192)	CC group, (n=192)	P value
Clinical pregnancy rate (%)	44.8 (86/192)	28.1 (54/192)	<0.001
Live birth rate (%)	36.5 (70/192)	22.4 (43/192)	0.002
Multiple pregnancy rate (%)	6.5 (12/192)	10.4 (20/192)	0.16

Endometrial thickness

Endometrial thickness at the time of hCG administration was significantly greater in the letrozole group (Table 4).

Table 4: Endometrial thickness.

Outcome	Letrozole group, (n=192)	CC group, (n=192)	P value
Endometrial thickness (mm)	8.7±1.3	7.5±1.2	<0.001

Table 5: Adverse effects.

Adverse effect	Letrozole group, (n=192)	CC group, (n=192)	P value
Hot flashes (%)	15.1 (29/192)	30.7 (59/192)	<0.001
Mood swings (%)	9.9 (19/192)	24.0 (46/192)	<0.001
Visual disturbances (%)	1.0 (2/192)	6.3 (12/192)	0.02

Adverse effects

Adverse effects were reported less frequently in the letrozole group compared to the CC group (Table 5).

Cost-effectiveness

The cost analysis indicated that letrozole was more cost-effective than CC, with lower overall treatment costs due to fewer cycles required for successful ovulation (Table 6).

Table 6: Cost-effectiveness analysis.

Parameters	Letrozole group, (n=192)	CC group, (n=192)	P value
Average cost per cycle (USD)	450	600	<0.001
Average total cost (USD)	1350	1800	<0.001

Patient satisfaction

Patient satisfaction was higher in the letrozole group, with a significant number of participants reporting preference for letrozole over CC due to fewer side effects and higher efficacy (Table 7).

Table 7: Patient satisfaction.

Outcome	Letrozole group, (n=192)	CC group, (n=192)	P value
Patient satisfaction score (1-10)	8.5±1.2	6.9±1.5	<0.001
Preference for future treatment (%)	80.2 (154/192)	58.3 (112/192)	<0.001

DISCUSSION

This RCT aimed to compare the efficacy and safety of letrozole versus CC for ovulation induction in women with PCOS. The results demonstrated that letrozole was superior to CC in several key outcomes, including ovulation rates, pregnancy outcomes, and patient satisfaction, while also showing a more favorable side effect profile.

The results of this study demonstrate that letrozole is more effective than CC in inducing ovulation in women with PCOS. Letrozole also leads to higher clinical pregnancy and live birth rates, with a lower incidence of adverse effects. Additionally, letrozole was found to be more cost-effective and resulted in greater patient satisfaction. These findings suggest that letrozole should be considered a first-line treatment for ovulation induction in women with PCOS, particularly for those who are resistant to CC.[8-10]

Ovulation rates

The primary outcome of ovulation was significantly higher in the letrozole group (76.0%) compared to the CC group (55.2%). These findings are consistent with previous studies that have suggested letrozole's superior efficacy in inducing ovulation in women with PCOS, particularly those who are CC-resistant. The mechanism by which letrozole achieves this may be attributed to its ability to reduce estrogen feedback on the hypothalamus, leading to increased follicle-stimulating hormone (FSH) secretion and more robust follicular development.[9]

Pregnancy outcomes

In addition to higher ovulation rates, the letrozole group also had significantly higher clinical pregnancy rates (44.8% vs. 28.1%) and live birth rates (36.5% vs. 22.4%) compared to the CC group. This aligns with the findings of Legro et al who also reported higher live birth rates with letrozole. The increased efficacy of letrozole in achieving pregnancy may be due to its ability to produce a more favourable endometrial environment and better-quality ovulatory cycles.[10-12]

Endometrial thickness

Endometrial thickness at the time of human chorionic gonadotropin (hCG) administration was significantly greater in the letrozole group (8.7 mm) compared to the CC group (7.5 mm). Adequate endometrial thickness is crucial for successful implantation, and letrozole's ability to maintain a thicker endometrium likely contributes to its higher pregnancy rates. CC, on the other hand, is known to have anti-estrogenic effects on the endometrium, which can adversely affect implantation.[12]

Adverse effects

Participants in the letrozole group reported fewer adverse effects than those in the CC group. Specifically, the incidence of hot flashes, mood swings, and visual disturbances were significantly lower in the letrozole group. These findings are consistent with the known side effect profiles of these medications. Letrozole, being an aromatase inhibitor, does not have the same anti-estrogenic effects on peripheral tissues as CC, leading to a more favorable side effect profile.[8,10-12]

Cost-effectiveness

The cost-effectiveness analysis revealed that letrozole was more cost-effective than CC, primarily due to the lower number of cycles required to achieve ovulation and pregnancy. This has significant implications for healthcare systems and patients, as the reduced treatment cost and higher efficacy make letrozole a more economical choice for ovulation induction in women with PCOS.[13]

Patient satisfaction

Patient satisfaction scores were higher in the letrozole group, with a significant number of participants expressing a preference for letrozole over CC. This preference was

largely driven by the higher success rates and fewer side effects associated with letrozole. High patient satisfaction is an important consideration in fertility treatments, as it can influence compliance and overall treatment experience.[14]

Limitations

Despite the robust findings, this study has several limitations. Firstly, the open-label design could introduce bias, although outcome assessors were blinded to treatment allocation to mitigate this risk. Secondly, the study was conducted at a single centre, which may limit the generalizability of the findings. Multicentre trials are needed to confirm these results across diverse populations and clinical settings.

CONCLUSION

The results of this study strongly support the use of letrozole as a first-line treatment for ovulation induction in women with PCOS. Letrozole not only demonstrated higher ovulation and pregnancy rates compared to CC but also showed a more favourable side effect profile and greater patient satisfaction. Given its cost-effectiveness and overall better performance, letrozole should be considered the preferred agent for inducing ovulation in women with PCOS, particularly in those who are resistant to CC. Further multicentre studies are warranted to validate these findings and establish comprehensive guidelines for the management of PCOS-related infertility.

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