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Original Research Article

The quest for better outcomes: a randomized controlled trial comparing letrozole versus clomiphene citrate in polycystic ovarian syndrome-related infertility

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ABSTRACT

Background: Infertility is a widespread concern, particularly among individuals with polycystic ovarian syndrome (PCOS). Clomiphene citrate (CC) has been a primary treatment for PCOS-related infertility, despite suboptimal pregnancy rates. Letrozole, an aromatase inhibitor, presents an alternative with potential advantages for improving pregnancy outcomes. This study aimed to rigorously compare letrozole and CC in the context of PCOS-related infertility, focusing on Bangladeshi women, adopting incremental dosing protocols, and examining endpoints to contribute valuable insights.
Methods: A randomized controlled trial was conducted at a tertiary care center in Bangladesh from July 2021 to June 2023. Participants included women aged 18-35 with anovulatory infertility due to PCOS. They were randomized into two groups: letrozole and CC. Treatments were administered following incremental dosing protocols, and outcomes included endometrial thickness, ovulation rate, mono-follicular development, pregnancy rate, and time to pregnancy.
Results: Out of 187 patients assessed for eligibility, 102 were enrolled, with 51 in each group. Demographics were comparable between groups. While endometrial thickness did not significantly differ between the groups, letrozole demonstrated a higher rate of mono-follicular development (72.55% versus 50.98%), a significantly higher pregnancy rate (47.06% versus 23.53%), and a shorter time to pregnancy (9.23 weeks versus 11.7 weeks) compared to CC.
Conclusions: This study suggests that letrozole may be a preferred option for ovulation induction in PCOS patients due to its superior pregnancy rates and shorter time to pregnancy compared to CC. However, limitations such as a relatively small sample size and variations in dosages should be considered. Further research is needed to validate these findings and address the evolving needs of patients with PCOS-related infertility.

Keywords: Infertility, PCOS, Letrozole versus clomiphene citrate, Ovulation induction, Pregnancy rates

INTRODUCTION

Infertility poses a profound challenge for many couples worldwide. Defined as one year of unprotected intercourse without conception, it is a distressing condition affecting numerous individuals.[1] Polycystic ovarian syndrome (PCOS) emerges as the leading cause of anovulatory infertility, responsible for 70% to 80% of cases attributed to anovulation.[2] Anovulatory women grappling with infertility are prime candidates for ovulation induction therapies. Clomiphene citrate (CC) has stood as the cornerstone among ovulation induction agents for quite some time.[3] Despite its commendable ovulatory rate, hovering around 85%, it falters when it comes to translating ovulation into successful pregnancies, with a meager 35% to 40% success rate.[3] This disconcerting discordance between robust ovulation and modest conception rates has been attributed to the peripheral anti-

estrogenic effects of CC and its protracted half-life of two weeks, which hinder optimal endometrial development during the latter stages of the menstrual cycle.[4]

The introduction of letrozole, an aromatase inhibitor, marked a significant development in the field. Since its adoption in 2001, letrozole has garnered attention as a potentially superior alternative to CC.[5] Initial concerns regarding potential congenital anomalies associated with letrozole use have been alleviated by robust multicenter studies.[6,7] Letrozole functions by curtailing estrogen synthesis, leading to a reduction in circulating estrogen levels. This action, in turn, releases the hypothalamic-pituitary axis from the negative feedback exerted by estrogen, resulting in a surge of follicle-stimulating hormone (FSH).[8] Unlike CC, letrozole does not exert anti-estrogenic effects on the endometrium, and its brief half-life of 48 hours facilitates rapid clearance from circulation. This, in effect, affords a later rise in estrogen levels, a pivotal factor in enhancing endometrial receptivity and, ultimately, pregnancy rates.[8] These distinctive pharmacological attributes have spurred extensive clinical investigation. Numerous clinical trials have juxtaposed the efficacy of letrozole and CC in women grappling with infertility due to PCOS.[3,4,9-13] These trials have also undergone rigorous scrutiny through a Cochrane systematic review and an individual patient data meta-analysis.[14,15] While Franik et al reported higher pregnancy and live birth rates with letrozole compared to CC, the overall quality of evidence remains a subject of debate, with questions raised about study quality, especially in domains related to randomization and allocation concealment.[14]

Moreover, the generalizability of findings is somewhat constrained by variations in dosing regimens employed across studies. Recognizing the need for more comprehensive investigations, particularly among treatment-naïve PCOS women, and the potential impact of regional disparities, we conducted this randomized controlled trial to meticulously compare the therapeutic efficacy of letrozole and CC. Focusing on Bangladeshi women grappling with anovulatory infertility attributed to PCOS, we implemented recommended incremental dosing protocols for both drugs and clearly defined study endpoints, endeavoring to contribute valuable insights to the field of assisted reproduction and address the evolving needs of our diverse patient population.

METHODS

Study design

This was a single-center, double-arm, assessor masked randomized controlled trial conducted at the Combined Military Hospital Chattogram, a tertiary care center in Bangladesh. The study was carried out between July 2021 and June 2023. Approval from the Institute Ethics Committee was taken.

Participants

Patients presenting with anovulatory infertility due to PCOS.

Inclusion criteria

Patients with age between 18 and 35 years, anovulatory infertility due to PCOS, polycystic ovarian morphology was ≥12 follicles of <10 mm and/or individual ovarian volume >10 ml, and patients with informed written consent were included.

Exclusion criteria

Patients with unfavorable premenstrual endometrial biopsy and tubal patency test, and abnormality in semen analysis of the partner, thyroid disease, hyperprolactinemia, any concurrent chronic disease, and treatment history with an ovulation-inducing agent within the past 6 months were excluded.

Randomization

Eligible patients were randomly assigned to one of two groups using a computer-generated randomization sequence. The randomization process was performed by an independent researcher not involved in the study. Group allocation was concealed in opaque sealed envelopes, which were opened sequentially at the time of patient enrollment. The radiologists performing the ultrasonogram for the assessment of the outcome were kept blinded to treatment allocation.

Interventions

In this study, participants in group 1 underwent ovulation induction using letrozole, while those in group 2 were treated with clomiphene citrate (CC), with a maximum of three treatment cycles or until achieving conception. Letrozole was administered at a daily dosage of 2.5 mg for five days, commencing from day 2 through day 6 of the menstrual cycle. If ovulation did not occur, the letrozole dosage was progressively increased by 2.5 mg in subsequent cycles, capped at a maximum of 7.5 mg. Conversely, CC was prescribed at a daily dose of 50 mg for five days, with an incremental rise of 50 mg per cycle, reaching a maximum of 150 mg if ovulation remained elusive. Serial transvaginal ultrasounds (TVS), conducted by a consultant, were scheduled on alternate days between day 11 and day 18. These assessments included the measurement of endometrial thickness (ET) and evaluations of dominant follicle size and number. ET was meticulously quantified from one echogenic border to the opposite end across the endometrial cavity, using a mid-sagittal image at the fundus as the reference point. Once the dominant follicle surpassed 18 mm in size, ovulation was induced by administering 5000 IU of human chorionic gonadotrophin (hCG) intramuscularly. Timed intercourse was advised, with a recommended window of 24 to 36

hours following hCG injection. ovulation as the presence of free fluid in the pouch of Douglas and collapsed follicle on TVS and/or day 21 serum progesterone value ≥3 ng/ml. Pregnancy was defined by detection of urinary human chorionic gonadotropin (hCG) after 7 days of missed period and or detection of gestation sac by ultrasound.

Outcome

The primary outcome is endometrial thickness.

Secondary outcomes were ovulation rate, mono-follicular development, pregnancy rate and time to pregnancy assessment.

Data collection

Data collected during this study included participant demographics, treatment group assignment, treatment dosages, ovulation monitoring results, and pregnancy outcomes. These data were crucial for assessing the effectiveness of the two different ovulation induction treatments and their respective impacts on ovulation and pregnancy rates. Statistical analysis was subsequently performed on this data to conclude the treatments' success rates and comparative outcomes.

Data analysis

Statistical analysis was conducted using statistical package for the social sciences (SPSS) software (version 23.0). Continuous data underwent normal distribution checks, with Student t-tests for normally distributed and Mann-Whitney U tests for non-normally distributed data. Chi-square tests assessed differences in categorical variables at a two-sided significance level of 0.05 to statistically significant. Time to pregnancy, measured in weeks from the start of ovulation induction, was compared using Kaplan-Meier plots and assessed for significance through log-rank tests.

Ethical considerations

Informed written consent was obtained from all study participants. Confidentiality of patient data was strictly maintained throughout the study. Ethical approval was obtained from the institutional review board (IRB) before the commencement of the study (IRB approval number: 1508). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

RESULTS

A total of 187 patients were assessed for eligibility (Figure 1). 85 patients were excluded according to the set criteria. A total of 102 patients were enrolled for randomization. There were 51 patients in each group. All patients were followed up to 1 year.

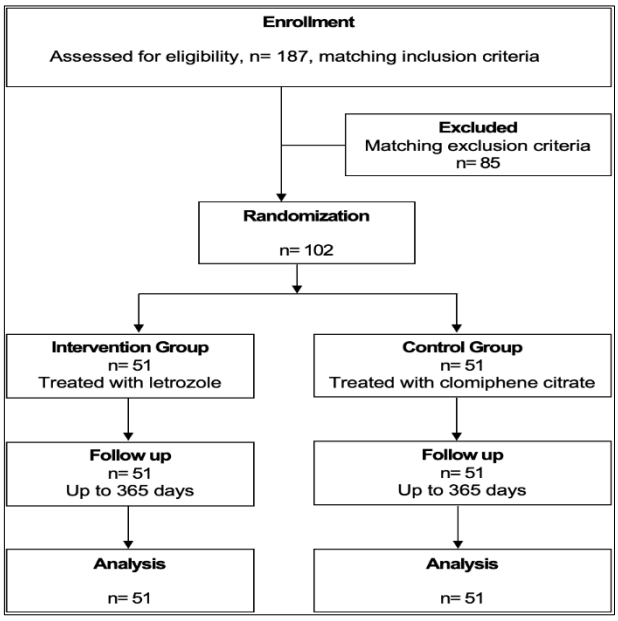

Figure 1: Consort flow chart.

The demographic characteristics of each group were comparable (Table 1).

Table 1: Demographic clinical data of the participants.

Parameters	Letrozole (n=51)	CC (n=51)	P value
Age (years)	24±5.23	25±4.62	0.22
BMI (kg/m^2)	23.9±3.34	22.8±3.78	0.123
Duration of infertility (years)	3.4±1.6	3.1±2.2	0.43
Primary infertility	33/51	35/51	0.67
Secondary infertility	18/51	16/51	0.67

Outcomes

In our comprehensive analysis, we examined key parameters to discern the differential effects of letrozole and clomiphene citrate (CC) within our study cohort. The mean endometrial thickness was meticulously measured, revealing values of 9.43±2.67 mm for the letrozole group and 9.21±2.56 mm for the CC recipients. Notably, these measurements failed to yield statistical significance (p=0.672). Regarding ovulatory outcomes, ovulation manifested in 88.24% of cycles initiated with letrozole and 84.31% of cycles induced with CC, with a statistically non-significant difference (p=0.565).

A particularly noteworthy observation pertained to mono-follicular growth, which prominently emerged in 72.55% of cycles stimulated by letrozole, in stark contrast to the 50.98% incidence observed in the CC group. Importantly, this disparity bore significant statistical weight (p=0.025). Furthermore, our scrutiny extended to pregnancy rates, which delineated a substantial discrepancy between the

two groups. The letrozole cohort exhibited a commendable pregnancy rate of 47.06%, whereas the clomiphene group recorded a comparatively lower rate of 23.53%, and this contrast achieved statistical significance (p=0.013) (Table 2).

Additionally, we rigorously evaluated the temporal aspect of our study, focusing on the duration between ovulation induction and the realization of conception. The results unveiled a markedly shorter timeframe (p<0.001) in the letrozole group, with a mean duration of 9.23±1.52 weeks, as opposed to the CC group, which registered a mean duration of 11.7±1.39 weeks (Table 2). These findings collectively illuminate the nuanced distinctions between the two interventions, underscoring the clinical significance of letrozole in our study population.

Table 2: Letrozole versus clomiphene citrate.

Parameters	Letrozole (n=51)	CC (n=51)	P value
Endometrial thickness (mm)	9.43±2.67	9.21±2.56	0.672
Rate of ovulation	45/51 (88.24)	43/51 (84.31)	0.565
Mono-follicular development	37/51 (72.55)	26/51 (50.98)	0.025
Pregnancy rate	24/51 (47.06)	12/51 (23.53)	0.013
Time to pregnancy (weeks)	9.23±1.52	11.7±1.39	<0.001

DISCUSSION

Our study had a simple goal: to compare two medicines, letrozole and clomiphene citrate (CC), to see which one is better at helping the lining of the uterus (endometrium) to grow. We wanted to know if there was any difference in the thickness of the endometrium when using these two medicines. We found that, on average, the endometrium was a bit thicker in the group of people who took letrozole (9.43±2.67 mm) compared to those who took CC (9.21±2.56 mm) But, the result was not statistically significant (p value=0.672). Other researchers, like Xi et al and Bansal et al, have found similar results.[17,19]

Other studies in the scientific literature have looked at this question, and they have given us mixed answers. Some studies say that letrozole makes the endometrium thicker than CC, while others say the opposite.[4,12,13,16,18] The reason for these different findings might be because the people in the studies were different. Their BMI, dosage, and duration of treatment varied between the studies. Also, the method of measurement of the endometrium could have influenced the results. Some even suggest that the endometrium might be thinner with letrozole because CC causes more than one follicle to develop, raising hormone levels and making the endometrium thicker.[4]

Our study also revealed noteworthy findings concerning ovulation rates, which showed remarkable similarity between the letrozole and clomiphene groups (88.24% and 84.31%, respectively). These rates exceeded those reported in existing literature. The difference in ovulation rates may be attributed to our use of a lower threshold for diagnosing ovulation based on serum progesterone levels (≥3 ng/ml), a departure from other studies that employed a higher threshold value.[4,17]

We meticulously adopted an incremental dosing strategy for the study drugs, progressively reaching the recommended maximum dosage in a clinical context. This practice was similar to Legro et al and Bansal et al.[9,19] In contrast, several prior studies either adhered to a fixed drug dosage for both agents or refrained from escalating to the recommended maximum.[3,4,11-13,16]

Within our investigation, we focused on mono-follicular development, revealing a significantly higher rate of mono-follicular development with letrozole (72.55%) in contrast to CC (50.98%). This finding aligns with Xi et al and Bansal et al, who similarly documented an elevated rate of mono-follicular development within the letrozole group, while Amer et al observed comparable outcomes between the two groups.[4,17,19] This discrepancy may be attributed to racial differences among the study populations and variations in the criteria employed for defining dominant follicles.

One of the most noteworthy findings of our study revolves around pregnancy rates, which revealed a substantial disparity. Specifically, we observed a 47.06% pregnancy rate in the letrozole group in contrast to a more modest 23.53% in the clomiphene group. This discrepancy was statistically significant (p=0.013). While it's essential to recognize that prior studies consistently reported higher pregnancy rates with letrozole compared to clomiphene citrate, only three of these studies identified this difference as statistically significant.[3,4,19]

Furthermore, our study stands out for its contribution in comparing the time-to-pregnancy following ovulation induction with study drugs—an essential patient-centered outcome that has been relatively underreported in the existing literature. Amer et al and Bansal et al have found similar results.[4,19]

Limitations

The sample size of our study was relatively small, potentially limiting the statistical power, especially for rarer outcomes. Additionally, the study's generalizability may be constrained, given the specific demographic studied, where factors like ethnicity and unique patient characteristics could affect treatment outcomes. Furthermore, our inclusion and exclusion criteria might have introduced selection bias, potentially limiting broader population applicability. Individual treatment dosages varied, not fully representing real-world clinical scenarios,

and the study's limited duration prevented a thorough examination of longer-term outcomes. Patient-centered aspects, such as quality of life, satisfaction, and adherence, were not extensively explored. Lastly, publication bias may have influenced the selection of studies for comparison in the existing literature. Despite these limitations, our study offers insights into the comparative effectiveness of letrozole and clomiphene citrate, which should be interpreted with caution, and future research should address these constraints for a more comprehensive understanding of clinical practice.

CONCLUSION

In conclusion, our study compares letrozole and CC for ovulation induction in anovulatory PCOS patients, shedding light on their comparative effectiveness. While we found no statistically significant difference in endometrial thickness (ET) between the groups, several clinically significant outcomes emerged. Both drugs exhibited comparable ovulation rates, but letrozole stood out with a significantly higher incidence of mono-follicular development, potentially promoting single, dominant follicle growth. Most notably, letrozole demonstrated a substantially superior pregnancy rate compared to CC, underlining its efficacy in translating ovulation into successful pregnancies. Additionally, our study delved into the time-to-pregnancy, revealing that letrozole achieved pregnancies significantly faster than CC, emphasizing its clinical relevance. However, we acknowledge limitations, including a relatively small sample size, potential selection bias, varied dosages, and a lack of participant blinding. Nevertheless, our findings support letrozole as a preferred option for ovulation induction in PCOS patients, particularly for its superior pregnancy rates and shorter time-to-pregnancy, warranting further comprehensive research to address evolving patient needs in clinical practice.

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