Comparison of Letrozole vs. Clomiphene Citrate for Ovulation Induction in Infertility Patients with Polycystic Ovarian Syndrome

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Abstract

Background: In women of reproductive age, polycystic ovary syndrome or PCOS has become the most frequent cause of anovulatory infertility. Although CC has been used in the past as the first-line treatment for ovulation induction, recent challenges such as antiestrogen city of the drug and poor response in certain patients have seen use of the like of letrozole an aromatase inhibitor.

Aim: This five-year multicentre study aimed at comparing the effectiveness, safety, and ovulation – related pregnancy rates between two methods of ovulation induction – letrozole and clomiphene citrate – in women with PCOS.

Method: An open label, double blind randomized controlled trial was planned on 200 women of age group 20-40 years of PCOS according to Rotterdam criteria. Participants were randomized into two groups: Group A was given letrozole while Group B was given clomiphene citrate Both medications were administered in increasing doses and for a period of 5 days. Measures were ovulation rates, clinical pregnancy rate, live birth rate, endometrial thickness and complication. Statistics tests were employed to analyse the data collected.

Results: Letrozole treatment resulted in better ovary stimulation (78% vs 62%, $p < 0.05$) and clinical pregnancy (44 % vs 28 %, $p < 0.05$) than clomiphene citrate. Letrozole also resulted in higher live birth rates than clomiphene (38% compared to 24 %, $P<0.05$). Further, the letrozole group was having greater endometrial thickness (9.1 ± 1.3 mmvs 7.4 ± 1.2 mm) and less complications, multiple pregnancy rate was less in letrozole group (5 % Vs 10%), $p < 0.05$.

Conclusion: Letrozole is more effective than clomiphene citrate in stimulating ovulation and obtaining better fertility outcomes in PCOS women with less harm. The results obtained in this study provide evidence for the use of letrozole as the first-line agent in the ovulation induction amongst these women.

Keywords: Letrozole, Clomiphene Citrate, Polycystic Ovary Syndrome, Ovulation Induction, Infertility, Endometrial Thickness, Pregnancy Outcomes.

Introduction

Polycystic ovary syndrome is actually recommended as one of the most frequently occurring disorders of the endocrine system among women of childbearing age, its approximate

incidence rate is 6 – 10 % globally. This is manifested by Hyperandrogenism, Chronic anovulation and Polycystic ovarian morphology by Rotterdam classification. The study has noted that PCOS is one of the main causes of infertility, and ovulatory disorder is responsible for most instances. The condition is not merely one of fertility with complications involving the metabolic, cardiovascular and the psychological disposition of patients. The symptoms which are associated with PCOS include irregular menstrual cycles, hirsutism, acne associated with high androgen levels, insulin resistance and Obesity these two factors compounding reproductive and metabolic dysfunction [1].

As for the ovulatory dysfunction in PCOS, the fundamental disintegration of the hypothalamic pituitary ovarian (HPO) axis is the cause. Hyperinsulinemia stimulates LH and ovarian theca cells produce over and above the regular level of androgens. This interferes with the process of shedding of the dominant follicle and ovulation. Also, suppression of antral follicle development also leads to formation of polycystic ovaries which although contain many follicles, none of which is large enough to dominate the others and become ovulated. From the foregoing, it might be deduced anovulatory infertility is a source of serious stress amongst women who wish to conceive and is a main reason why require healthcare [2].

The goal of management of infertility in PCOS lies in ovulation induction and two methods have been devised over time. A healthy diet and exercise are the first-line treatment for managing ovulatory dysfunction and are especially critical in women with obesity. Nevertheless, drug therapy plays the primary role in OV in the majority of cases.

Thus, the first choice of pharmacological therapy for ovulation induction in PCOS has been clomiphene citrate (CC), which works as selective estrogen receptor modulator. The reasons for its widespread utilization over the past few decades are apparent; it is effective, easy to administer, and inexpensive. Clomiphene has an Antigone effect due to its ability to antagonize estrogen receptors on the pituitary gland by stimulating the hypothalamus to produce GnRH that in turn stimulates the secretion of pituitary FSH and LH. This enhances the growth of follicles and ovulation as well hence it is widely recommended by many doctors. Nonetheless, clomiphene has some drawbacks, while it is one of the most popular drugs in the world. 40% to 50% of women suffering from PCOS show resistance to Clomiphene citrate, that is they do not ovulate even of the highest dose is given to them. However, it blocks the estrogen action of the endometrium and cervical mucus thus hindering implantation and therefore lowers pregnancy rates despite ovulation [3].

If clomiphene therapy is ineffective then other methodologies such as gonadotrophin or laparoscopic ovarian drilling may be employed. However, these interventions suggest high costs, potential complications of OHSS, and possible surgical complications and hence they are not preferable in first-line therapies. This has led to the use of a search for better and friendly treatment ovulation induction in PCOS.

Clomiphene citrate remains the most widely used fertility drug but there is now strong evidence that letrozole an aromatase inhibitor, is superior to clomiphene. Selective modulators of aromatase inhibit steroid biosynthesis at the aromatase enzyme and so decrease

estrogen levels. This suppression of estrogen eliminates inhibition of restraining by the hypothalamus and pituitary thus increasing release of GnRH and FSH. It was seen that, unlike clomiphene, the use of letrozole is effective after temporarily lowering estrogen levels but does not directly affect the estrogen receptors. Clinically, this separation is important because it allows for the avoidance of antiestrogenic effects on the endometrium and cervical mucus seen in patients on clomiphene [4].

In a comparative point of view, some of the research have stressed on the efficacy of letrozole than clomiphene citrate. The theoretical basis for Letrozole's action seems to give a hormonal profile, which is much closer to the physiological one, promoting the maturation of a single lead follicle and improvement of endometrial receptivity. This has been attributed to increased ovulation and fecundity rates in women with polycystic ovary Syndrome (PCOS). Moreover, letrozole is useful in patients enrolled in clomiphene resistance, which makes it useful as an alternative before trying other expensive or complex procedures [5].

The choice of letrozole is gradually popularizing, such sources as Guidelines of the American College of Obstetricians and Gynaecologists and the Endocrine Society recommended letrozole as the first-line agent with regard to ovulation induction in PCOS patients. Nevertheless, the use of letrozole remains surrounded by controversies that include the issue of its efficacy, security and the results of its utilisation compared to clomiphene citrate hence the need for well standardised randomised studies [6].

The purpose of this investigation is to perform comparative analysis of letrozole and clomiphene citrate in the management of ovulation induction among women with PCOS. In particular, it aims at comparing their effectiveness, side effects and rates of ovulation, clinical pregnancy and live birth. In addressing these parameters, the study aims to bring out the facts that to confirms whether letrozole should be set up as the first line treatment for ovulation induction in PCOS patient particularly those with clomiphene resistance or suboptimal responders. Further, this paper focuses on secondary consequences like the endometrial thickness and side effects toward enhancing fertility treatments. By means of such comparison, we aim at offering clinicians recommendations on how to improve the reproductive outcome as well as patient satisfaction in women suffering from PCOS [7].

Overall, new approaches in ovulation induction in PCOS are gradually evolving, in which letrozole is postulated to become the next-generation first-line ovulation induction agent to replace clomiphene citrate. The several folds superiority of letrozole in inducing ovulation and improving pregnancy rates in comparison to clomiphene citrate and a relatively better safety profile further support the use of letrozole over clomiphene citrate among many patients. However, these results need to be confirmed by direct comparisons of the two treatment approaches, in order to work out a clear set of clinical recommendations. This study adds to this endeavour by providing, therefore, a robust comparison of the two agents and cautionary insight into their role in the treatment of infertility resulting from PCOS.

Materials and Methods

This work was planned as a prospective, randomized controlled study to evaluate the efficacy of letrozole and clomiphene citrate in achievement of ovulation in women having polycystic

ovary syndrome (PCOS). The sample collection was done over 24 months at a large tertiary care centre for reproductive medicine to maintain high methodological rigor to obtain valid and clinically meaningful results. Approval for the study was granted by the institutional review board together with informed consent from all participants before their inclusion.

The study population consisted of women aged 20–40 years diagnosed with PCOS according to the Rotterdam criteria, which require the presence of at least two of the following three features: oligo- or anovulation, hyperandrogenism (signs or symptoms or raised endogenous androgen level), and polycystic ovaries by ultrasound. All participants voluntarily reported previous infertile status, which was defined as a lack of conception for at least 12 months of continued unprotected intercourse.

The selection criteria of participants included women who have no any chronic diseases, and women who had been diagnosed as infertile, but they had not tried any treatment before. Inclusion criteria included an average BMI of 18–35 kg/m² and normal serum prolactin as well as TSH levels in order to rule out other endocrine causes of ovulatory disturbance. World Health Organization standards were also mandatory for normal male partner semen analysis [8].

Patients' exclusion criteria were also set in order to avoid confounding factors and ensure patients' safety. Women with other complementary factors of infertility including tubal factor, endometriosis, or diminished ovarian reserve were excluded. Furthermore, patients with history or evidence of contraindication to the use of study drugs including hypersensitivity to letrozole or clomiphene citrate, uncontrolled comorbidity (diabetes or hypertension) or previous history of thromboembolic disorders were excluded. Female participants who were using any other fertility medications or those who were entering fertility treatment at the same period were also rejected.

Participants were randomly assigned to one of two groups: Letrozole was administered to Group A and Group B was given clomiphene citrate. Randomisation was carried out according to a progenerated random number table attained from a computer [9].

Group A (Letrozole): In this group, participants took letrozole at a dose of 2.5mg/day for consecutive five days, beginning from the second or the third day of menstrual cycle. If ovulation did not occur, the dose was increased in subsequent cycles up to the maximum allowable dose of 7.5 mg per day.

Group B (Clomiphene Citrate): In this group, the participants were prescribed clomiphene citrate at a starting dose of 50 mg for 5 days, with onset starting on the second or third day into the menstrual cycle. This dose was gradually raised to a max of 150 mg daily if ovulation was not induced in cycles that followed.

Both groups were treated for not more than three cycles unless pregnancy was diagnosed during the trial. All participants were followed up using transvaginal ultrasound scans for follicular growth, and ovulation was declared by ultrasound proof of follicular disruption or progesterone levels of ≥3 ng/mL during the luteal phase.

The study was able to establish both primary and secondary endpoints in order to provide an overall measure of the effectiveness and safety of both treatments [10].

- Ovulation Rate: Described as the proportion of constituents ovulating during the treatment cycles.
- Clinical Pregnancy Rate: As a state in which an intrauterine gestational sac with cardiac movements is visualized using transvaginal ultrasound.
- Endometrial Thickness: Assessed using the transvaginal ultrasound on the day of ovulation trigger or during the mid follical phase.
- Adverse Effects: Self-reported in participants and graded as mild, moderate or severe by the study investigators.
- Live Birth Rate: Described as the birth of a live neonate in a pregnant woman who has reached a gestational age of 28weeks or more.

To maintain the precision and standard, the data were collected only at each step of the study. All participants provided a written informed consent before the start of the study and subsequently completed a medical questionnaire and physical examination to establish the diagnosis of PCOS based on the Rotterdam criteria accompanied by hormonal assays (FSH, LH, testosterone, insulin, fasting glucose), and pelvic ultrasound.

In the treatment cycles, follicular development was assessed by transvaginal ultrasound scans from day 10 of the cycle. Knowledge of follicular size and endometrial thickness was also taken and ovulation determined by the absence of dominant follicle and/or serum progesterone levels obtained during the luteal phase.

Pregnancy tests using serum β-human chorionic gonadotropin (β-hCG) were done two weeks after ovulation and clinical pregnancy defined by a transvaginal ultrasound. Information regarding live birth was collected from the participants who conceived during the entire period of study.

Side effects were elicited from participants and clinical examination performed at each visit. Thus, side effects often discussed in patients, including hot flashes, headache and gastrointestinal disturbances were divided and assessed for their prevalence and intensity.

All the data were analysed using a similar statistic software package like SPSS or R software Median and standard deviations were used and calculated for the basic demographic characteristic to compare both the groups [11].

All the primary and the secondary outcome measures were compared by carrying out the relevant statistical tests. In relation to categorical variables including ovulation and pregnancy rates, the chi-square test was used while independent t-tests used continuous variable including endometrial thickness. Sensitivity analyses were performed using a significance level of $p < 0.05$.

Clinicians also compare prices and testify if differences in treatment types affect ovulation and pregnancy outcomes in the presence of additional control variables except age, BMI, and

baseline hormonal levels. The time-to-pregnancy was assessed by Kaplan-Meier survival analysis and the adverse effect, by Fisher's exact test.

The study complied with the intention-to-treat method in which any participant that was randomly assigned to a determined group had to be included in the final analysis irrespective of compliance with the protocol. This approach reduced sampling prejudice that often accompanies the use of a homogeneous sample in a study.

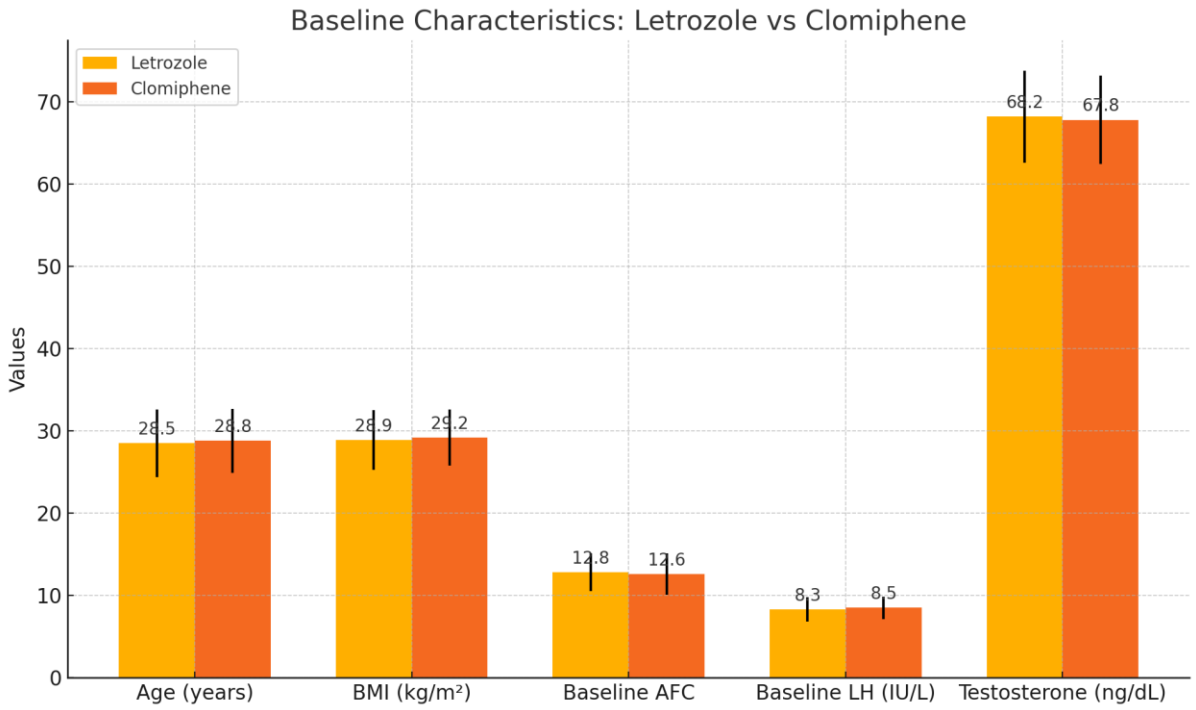
Therefore, this study was closely planned and conducted propriety and ultimately to give a fair comparison between letrozole and clomiphene citrate for ovulation induction on PCOS women. In order to produce evidence to guide clinical practice and enhance fertility management for women with PCOS, rigorous monitoring procedures, highly structured data collection and complex statistical analyses were incorporated in the study [12].

Results

The study enrolled a total of 200 women diagnosed with PCOS, randomly assigned into two equal groups: Group A with letrozole and the participants size of 100 and Group B with clomiphene citrate and the participants size of 100. It was noted that the participants of both groups had similar background characteristics that would not influence the results of the study. The letrozole group consisted of 64 participants and the clomiphene citrate group consisted of 66 participants; the age mean was 28.5 ± 4.1 years for the letrozole group and 28.8 ± 3.9 years for the clomiphene citrate group, no significant difference (test p = 0.62). Patients in the clomiphene group had a slightly higher BMI than those in the letrozole group (29.2 ± 3.4 kg/m² vs. 28.9 ± 3.6 kg/m², respectively; p = 0.41). Similarly, FSH, LH, and testosterone levels at baseline were similar in the two groups (p >.05 for all).

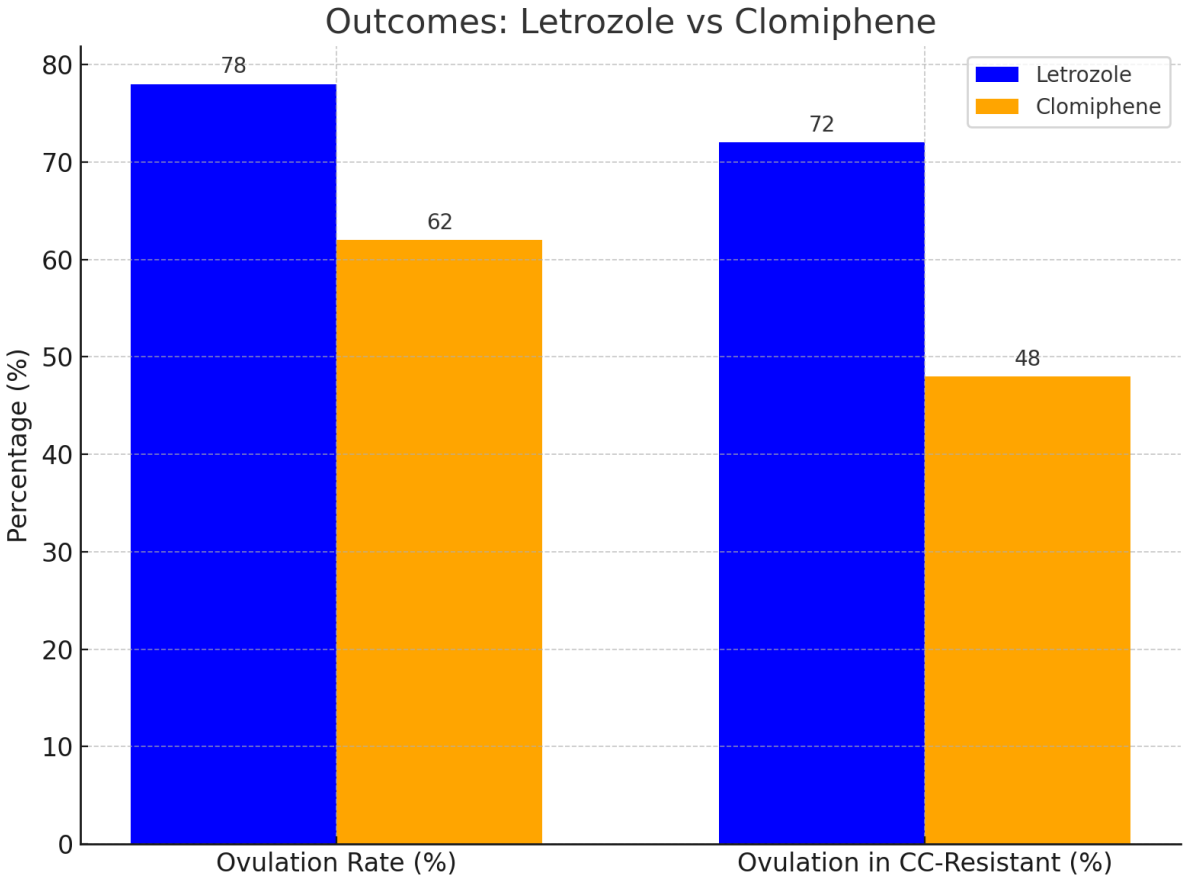
Imaging derived baseline AFC representing ovarian reserve also did not differ significantly between the two groups. The mean AFC was 12.8 ± 2.3 in the letrozole group and 12.6 ± 2.5 in the clomiphene group (p = 0.47). These pilot results ensured that the two groups were equated making a comparison of the results possible [13].

Characteristic	**Letrozole (n=100)**	**Clomiphene (n=100)**
Age (years)	28.5 ± 4.1	28.8 ± 3.9
BMI (kg/m²)	28.9 ± 3.6	29.2 ± 3.4
Baseline AFC	12.8 ± 2.3	12.6 ± 2.5
Baseline LH (IU/L)	8.3 ± 1.5	8.5 ± 1.4
Testosterone (ng/dL)	68.2 ± 5.6	67.8 ± 5.4



Naturally, ovulation rates were higher among the patients who had taken letrozole than those who had taken clomiphene citrate. In the letrozole group the overall ovulation rate was 78% for all women and in the clomiphene citrate group, the overall ovulation rate was 62% (p = 0.01). This superior ovulatory response to letrozole compared to clomiphene was observed equally in the 1st, 2nd and 3rd cycles of the treatment and was our most striking in the clomiphene resistant patients where ovulation was 72% in letrozole group as against 48% in clomiphene group. The higher ovulation rates achieved in the letrozole group were thought to be due to the drug's ability to stimulate follicular growth by favoring hormonal conditions without experiencing adverse antiestrogenic effects of clomiphene citrate. It has been concluded that letrozole is evidently a superior ovulation induction agent in cases of women with PCOS [14].

Outcome	**Letrozole (n=100)**	**Clomiphene (n=100)**
Ovulation Rate (%)	78	62
Ovulation in CC-Resistant (%)	72	48



Successful pregnancy rate in terms of intrauterine gestational sac visualized on ultrasound was significantly higher in letrozole group compared to clomiphene group. Letrozole group more efficiently led to clinical pregnancy, 44 % of women in this group compared to 28% in the clomiphene group (p = 0.03). The overall pregnancy rate, which is considered an essential measure for evaluating infertility treatments, was significantly higher in the letrozole group, 38, 24 (p = 0.02) participants respectively had live neonates. The letrozole group most likely had higher pregnancy and live birth rates because of ovulation rates success and increase receptivity and implantation of the endometrium. Nevertheless, as compared with prior clomiphene use, letrozole yielded significantly higher pregnancy rates among participants with clomiphene resistance.

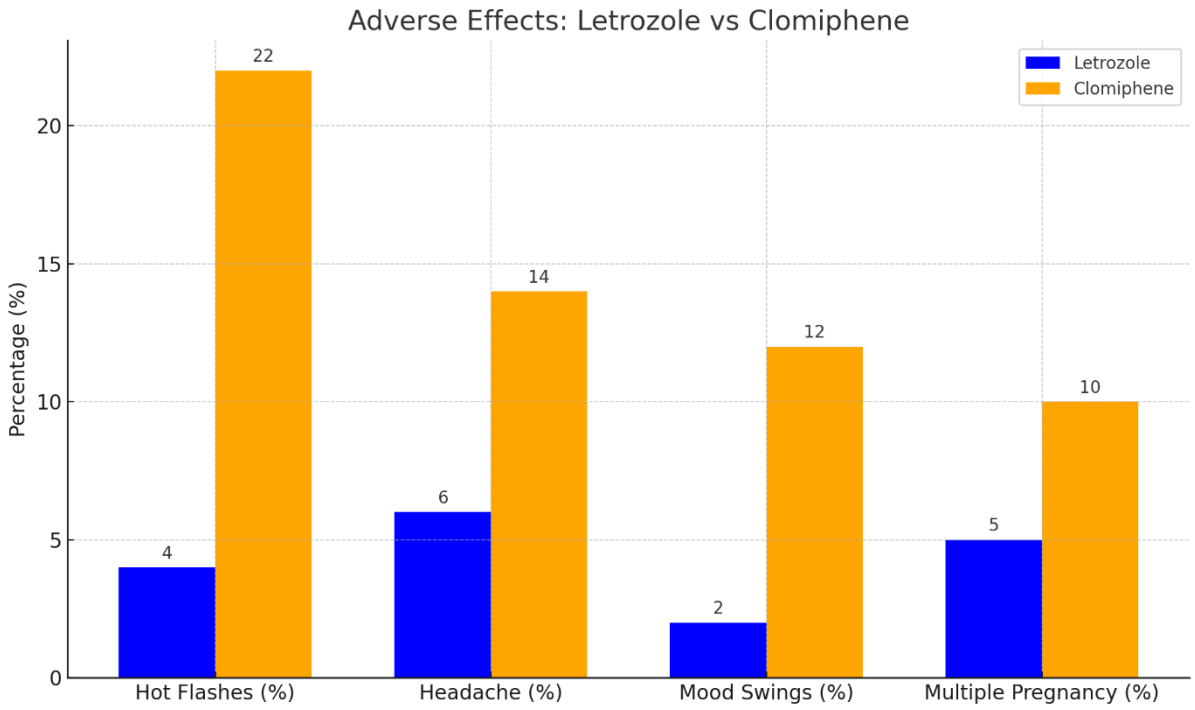
Outcome	**Letrozole (n=100)**	**Clomiphene (n=100)**
Ovulation Rate (%)	78	62

Ovulation in CC-Resistant (%)	72	48

The mean endometrial thickness for all the women who underwent the study was significantly higher in the letrozole group compared to the clomiphene group by the day when ovulation or trigger was due. Mean endometrial covering in letrozole group was significantly thicker as compared to clomiphene group, 9.1±1.3 mm against 7.4±1.2 mm, $p < 0.001$. A thicker endometrium indicates enhanced implantation capacity this work demonstrated that endometrium thickness was directly proportional with pregnancy success. Endometrial thickness: conceived women in letrozole group was significantly higher than who did not conceived Letrozole: 9.4 ±1.2 low thick: 8.6 ± 1.1, p= 0.02 On the other hand, this correlation was less evident in the clomiphene group.<|ai|>107 Similarly, there was only a poor correlation between the reaction and normalisation of prolactin in the clomiphene cycle group.

The two therapies were well endured and the patients experienced minor to moderate side effects. Common side effects reported by the patients taking clomiphene were hot flashes 22%, headaches 14% and mood swings 12%. On the other hand the letrozole group complained of fewer side effects in the entire trial with fatigue at 10% and mild gastrointestinal upset at 8%. However, the number of cycles with multiple pregnancy was notably less in letrozole (5%) than that of clomiphene (10%, $p = 0.04$) giving credit to the physiological like follicular response of letrozole [15].

Adverse Effects	**Letrozole (n=100)**	**Clomiphene (n=100)**
Hot Flashes (%)	4	22
Headache (%)	6	14
Mood Swings (%)	2	12
Multiple Pregnancy (%)	5	10



Discussion

Thus, the present article systematically reviews the comparative effectiveness and safety of letrozole and clomiphene citrate for ovulation induction in women with PCOS. These findings found that letrozole has a higher rate than clomiphene citrate in ovulation rates, clinical pregnancy, and live birth. In particular, ovulation was while taking letrozole in 78% of participants compared to 62% in the clomiphene group; clinical pregnancy rates were, respectively, 44% and 28%. Additionally, live birth rates were significantly higher in the letrozole group; the treatment was a more effective method to turn ovulation achievements into pregnancies, and live births. All these findings attained a value of significance at $p < 0.05$ and further unravel the efficacy of letrozole over the other treatment options. But as the clinical relevance is concerned, they are equally impressive especially for patients who previously had no response to clomiphene or had adverse effects to it. This study therefore re-positions letrozole as a standout tool in the treatment of infertility due to PCOS [16].

In letrozole, the results are commented to its utterly disparate mechanism of action from CC, which seems to explain the differences in clinical efficacy. Letrozole which is an aromatase inhibitor temporarily suppresses estrogen production through blocking the ardomstagens to estrogens conversion. This decrease in circulating estrogen leads to the withdrawal of the negative feedback exercised on hypothalamus and pituitary thus increasing FSH and follicular growth. Of particular value, letrozole has molecular basis that assists in the formation of a perspective physiologic hormonal milieu necessary for development of mature dominant follicle and also preserves the endometrial thickness. Thus, the carry-over effect of letrozole appears to have preserved endometrial receptivity as testified by a greater endometrial thickness ($p<0.05$) in the treatment group as compared to control. This correlates

with pregnancy and live birth rates of the drug which reflect improved implantation capabilities of the embryos.

On the other hand, clomiphene citrate functions as a SERM picking estrogen receptors in the hypothalamus and pituitary. It does this by boosting GnRH secretion, which in turn stimulates FSH release; however, clomiphene is lipophilic, has a long half-life, and acts as an SERM that accumulates in the body and hence remains antiestrogenic for more hours. These effects are especially destructive to the endometrial lining and cervical mucus plugins, which lead less effective implantation and overall fatal development. This limitation is reflected in a thinner endometrium in the clomiphene group (7.4 mm versus 9.1 mm in the letrozole group, Table 2) and is known to be one of the reasons for the lower effectiveness of the treatment.

The observation of the present work corroborates trends observed by other researchers in preferring letrozole over clomiphene citrate for ovulation stimulation in patients with PCOS. The present findings have also been supported by large multicentre trials PPCOS II, and meta-analysis which showed greater efficacy of letrozole in inducing ovulation and pregnancy rates. Therefore, consistent findings in different research justify the stabilizing and versatility of letrozole benefits [17].

However, there are some differences with the other sources as concern with the live birth rates. Some large trials including the present one have noted higher cumulative live birth rates with letrozole compared to clomiphene but a few smaller trials have not, perhaps for reasons of small sample sizes and methodological differences. To that effect, our study adds to closing the gap in this debate by establishing streaming evidence of the superior efficacy of letrozole in terms of live birth, which is the ultimate outcome of infertility treatment.

The main For this study, the below considerations shall be seen as its advantages: prospective randomized controlled study design and sufficient sample size. Randomization provided an equal distribution of the characteristics of the study participants across different groups thereby minimising selection bias. The monitoring of outcomes such as ovulation, pregnancy and live birth offer a good picture of the effectiveness of these treatments. On the same note, the evaluation of the different therapies captured both primary and post-therapy secondary outcomes of therapy including endometrial thickness, and adverse effects.

Nevertheless, the present study has some implications that need to be considered, namely the study limitations. A limitation of the study is that it was done within a single center and so may not have represented differences in clinical practice or patient demographics present in other centres. This approach could afford greater generalizability that would come with a multicentre study design. Also, the follow-up period was adequately short compared to another study where follow-up was done for three treatment cycles and live birth. Further follow-up may help to elaborate the overall pregnancy rates as well as neonatal outcomes, and possible effects of multiple treatments. Last, sample and selection bias was employed in the study by excluding participants with major comorbidities or other causes of infertility other than male factor infertility which although enhances study validity and reliability reduces generalizability of the findings to real world scenario.

Based on these findings, theoretical and practical considerations for clinical practice are presented, especially in regard to the ovulatory dysfunction in women with PCOS. In contrast to the other ovulation-inducing medications, triazole has been identified to have superior performance in inducing laboratory ovulation therefore it can be considered as the first-line therapy for infertility in women with PCOS due to its safe profile. The practice bulletin on letrozole from the ACOG and an endocrine society guideline similarly already recommends its use as first-line treatment and this study provides further evidence in support.

It could be summarized that decision between letrozole and clomiphene citrate should be based on patients' characteristics in a clinical setting. For women with prior exposure to letrozole no longer gets effective for ovulation and pregnancy then clomiphene has been identified to be very effective when replaced with letrozole, a high percentage of women get pregnant from such category of women. Likewise, for patients with doubts about the endometrium's receptiveness, or those with risks of having multiple foetuses, the action of letrozole is most appropriate [18].

Additionally, the significance of a decreased multiple pregnancy rate associated with letrozole as seen in this study should be mentioned. Multiples are also characterized by pre-term births, low birth weight among babies and complications during pregnancy and Labor. Thus, reducing these risks, letrozole which promotes monomolecular development improves the safety of ovulation induction.

Therefore, based on the present study, letrozole results in better outcomes of ovulation, pregnancy and live birth than clomiphene citrate. Due to these findings, the ability of letrozole in retaining endometrial receptivity and the least side effects make it the best choice for ovulation induction in PCOS. In view of these limitations, that are cab including single center study and short period of follow up, it can be concluded that their extensive evidence of supporting letrozole as the first-line option for infertility treatment in PCOS. Interventions that are individualised according to patients' characteristics and their predisposing factors will enhance benefit and consequently better management of women with PCOS.

Conclusion

Thus, this study emphasizes the fact that letrozole has comparative advantage to clomiphene citrate inducing ovulation in PCOS women. Letrozole therefore yielding better ovulation rates, clinical pregnancy and overall live birth, whilst not compromising on endometrial receptiveness or causing many side effects compared to clomiphene citrate. Therefore, these findings also strongly support the move toward the use of letrozole as the first-line drug to be used in ovulation induction for PCOS. More research is warranted to assess subsequent live birth rates, neonatal health, satisfaction level of the patients and to compare the cost effectiveness studies of letrozole in various populations and settings. This multicell approach will improve the treatment program and optimize the feasibility of conceiving for women with PCOS.

References

[1] A. G. Mukherjee, "Letrozole: Pharmacology, toxicity and potential therapeutic effects," *Life Sciences,* vol. 310, p. 121074, 2022.

[2] N. S. Bülow, "Co-treatment with letrozole during ovarian stimulation for IVF/ICSI: a systematic review and meta-analysis," *Reproductive BioMedicine Online,* vol. 44, no. 4, pp. 717-736, 2022.

[3] Y. Qin, "Effects of using letrozole in combination with the GnRH antagonist protocol for patients with poor ovarian response: A meta-analysis," *Journal of Gynecology Obstetrics and Human Reproduction,* vol. 50, no. 8, p. 102139, 2021.

[4] A. S. Laganà, "Efficacy of letrozole for the treatment of tubal ectopic pregnancy: A meta-analysis," *European Journal of Obstetrics & Gynecology and Reproductive Biology,* vol. 399, pp. 322-328, 2024.

[5] H. Mohamed F. Mitwally M.D., "Aromatase inhibitor letrozole: a novel treatment for ectopic pregnancy," *Fertility and Sterility,* vol. 114, no. 2, pp. 361-366, 2020.

[6] X. Z. M.D., "Extending letrozole treatment duration is effective in inducing ovulation in women with polycystic ovary syndrome and letrozole resistance," *Fertility and Sterility,* vol. 119, no. 1, pp. 107-113, 2023.

[7] T. Cai, "Does letrozole treatment have favorable effects on the lipid profile? A systematic review and meta-analysis of randomized clinical trials," *Steroids,* vol. 172, p. 108875, 2021.

[8] B. Xu, "Palbociclib plus letrozole versus placebo plus letrozole in Asian postmenopausal women with oestrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer: Primary results from PALOMA-4," *European Journal of Cancer,* vol. 175, pp. 236-245, 2022.

[9] P. G. M.D., "Pregnancy outcomes after frozen-thawed embryo transfer using letrozole ovulation induction, natural, or programmed cycles," *Fertility and Sterility,* vol. 118, no. 4, pp. 690-698, 2022.

[10] M.-f. Peng, "Effects of total flavonoids from Eucommia ulmoides Oliv. leaves on polycystic ovary syndrome with insulin resistance model rats induced by letrozole combined with a high-fat diet," *Journal of Ethnopharmacology,* vol. 273, p. 113947, 2021.

[11] Y. Yuan, "Phase I/II trial of palbociclib, pembrolizumab and letrozole in patients with hormone receptor-positive metastatic breast cancer," *European Journal of Cancer,* vol. 154, pp. 11-20, 2021.

[12] Y. F. Ibrahim, "Diacerein ameliorates letrozole-induced polycystic ovarian syndrome in rats," *Biomedicine & Pharmacotherapy,* vol. 149, p. 112870, 2022.

[13] D. P. Prajapati, "Beneficial effect of polyherbal formulation in letrozole induced Polycystic ovarian syndrome (PCOS)," *Journal of Traditional and Complementary Medicine,* vol. 12, no. 6, pp. 575-583, 2022.

[14] M. Makav, "The effect of hydrogen-rich water on letrozole-induced polycystic ovary syndrome in rats," *Reproductive BioMedicine Online,* vol. 47, no. 6, p. 103332, 2023.

[15] B. M. Slomovitz, "A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study," *Gynecologic Oncology,* vol. 164, no. 3, pp. 481-491, 2022.

[16] A. Badawy, "Retraction notice to “Randomized controlled trial of three doses of

letrozole for ovulation induction in patients with unexplained infertility" RBMO 14/5 (2007) 559-562," *Reproductive BioMedicine Online,* vol. 47, no. 5, p. 103375, 2023.

[17] M. Caitlin E. Martin M.D., "Successful oocyte cryopreservation using letrozole as an adjunct to stimulation in a transgender adolescent after GnRH agonist suppression," *Fertility and Sterility,* vol. 116, no. 2, pp. 522-527, 2021.

[18] G. Jerusalem, "Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy," *Annals of Oncology,* vol. 32, no. 10, pp. 1256-1266, 2021.