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Research Article

The Efficacy of Letrozole vs. Clomiphene Citrate in Ovulation Induction for Women with Polycystic Ovary Syndrome (PCOS)

Mubashira Malik[1], Guloona Sajjad[2], Saliha Javed[3]*, Hassan Ahmed[4], Anam Qazi[5]

1. *MBBS, Gajju Khan Medical College, Swabi, Pakistan*
2. *MBBS, Pak International Medical College, Khyber Medical University, Peshawar, Pakistan*
3. *MBBS, Rehman Medical College, Khyber Medical University, Peshawar, Pakistan*
4. *MBBS, Abbottabad International Medical Institute, Abbottabad, Pakistan*
5. *MBBS, Khyber Girls Medical College, Peshawar, Pakistan*

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Abstract

Introduction: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder that significantly impairs female fertility. Clomiphene Citrate (CC) has long been considered the first-line agent for ovulation induction, while Letrozole (LTZ), a selective aromatase inhibitor, has emerged as a promising alternative. This study aimed to compare the clinical efficacy of LTZ and CC in women with PCOS attending tertiary care centers in Peshawar, Pakistan.

Materials and Methods: A prospective randomized controlled trial was conducted over a 12-month period involving 158 women diagnosed with PCOS based on the Rotterdam Criteria. Participants were randomly assigned to receive either LTZ (2.5–7.5 mg/day) or CC (50–150 mg/day) from cycle days 3 to 7. The primary outcomes were ovulation rate, clinical pregnancy rate, and endometrial thickness. Data were analyzed using the chi-square test, independent t-test, and binary logistic regression to evaluate treatment efficacy and predictors of response.

Results: Ovulation was confirmed in 86.1% of women treated with Letrozole versus 67.1% in the Clomiphene Citrate group ($p = 0.002$), indicating a statistically significant difference in ovulatory response. The clinical pregnancy rate was higher in the LTZ group (39.2%) than in the CC group (30.4%), although this difference did not reach statistical significance ($p = 0.141$). Endometrial thickness was significantly improved in the LTZ group (mean 9.4 mm) compared to the CC group (mean 8.1 mm) ($p = 0.003$). Both medications were well tolerated, with a slightly lower incidence of adverse effects such as hot flashes and abdominal discomfort in the LTZ group.

Conclusion: Letrozole demonstrated superior efficacy over Clomiphene Citrate in promoting ovulation and enhancing endometrial development among women with PCOS. Although the improvement in pregnancy rate did not achieve statistical significance, the observed trend may have clinical relevance. Further large-scale, multi-center studies are warranted to confirm these findings and evaluate live birth rates and long-term safety.

* *Corresponding Author:*
Saliha Javed
MBBS, Rehman Medical College, Khyber Medical University, Peshawar, Pakistan
Email: saliha.javed25@gmail.com

Introduction

PCOS exists as one of the most common endocrine illnesses in women in the reproductive period which presents with three main symptoms including persistent anovulation together with elevated male hormones along with ovarian cyst patterns [1]. PCOS diagnostic criteria determine the global prevalence which extends between 6% to 20% of affected women [2].

The prevalence rate of this multifactorial disorder in women aged 15–49 is estimated to reach one in five cases according to Pakistani research reports [3]. PCOS creates reproductive difficulties through anovulation that causes infertility while exposing patients to severe future medical threats, including insulin resistance, metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and psychological issues. Recent national surveys estimate that infertility affects 21–24% of Pakistani couples, yet less than 35% of public hospitals offer dedicated ovulation-induction services, creating unmet need in resource-constrained settings. Robust local data comparing LTZ and CC are therefore essential to guide cost-effective treatment algorithms [4].

The main goal of ovulation induction therapy for women with PCOS is to create normal menstrual cycles and enhance fertility success [5]. Since its introduction many decades ago Clomiphene Citrate (CC) became the primary medication for this treatment procedure [6]. The selective estrogen receptor modulator hormone CC blocks hypothalamic estrogen signaling to enhance FSH and LH hormone secretion [7]. Clomiphene Citrate provides proven safety to patients because it is easily accessible, yet it causes unwanted endometrium changes and blocks estrogen to cervical mucus and has high ovulation rates which results in "Clomiphene resistance" [8].

Modern medicine has validated Letrozole as a beneficial treatment approach for inducing ovulation in PCOS patients [9]. The endocrine condition for follicular development improves when Letrozole stops aromatase from transforming androgens into estrogens because this medication blocks the aromatase activity [10]. Medical research shows that using Letrozole could produce superior ovulation outcomes and better live birth statistics than Clomiphene especially for patients who failed to respond to Clomiphene [11]. The lower number of anti-estrogenic side effects connected to Letrozole makes this drug an appealing choice during clinical application [12]. Letrozole shows expanded evidence of effective yet inconsistent treatment guidelines between regions alongside physician, patient and institutional choice determining the drug-selection process between Letrozole and Clomiphene. The identification of appropriate and affordable treatment for ovulation induction in Pakistani women with PCOS becomes essential because these settings combine limited follow-up capabilities with cost-sensitive protocols.

The research demonstrates Letrozole produces better outcomes than Clomiphene Citrate but local studies evaluating these drugs specifically for Pakistani women with PCOS remain scarce so local clinical choice data remains inadequate. This research seeks to evaluate the ovulation-inducing effectiveness between Letrozole and Clomiphene Citrate for women diagnosed with PCOS.

Materials and Methods

Study Design and Setting

This prospective, randomized controlled trial was conducted from April 2022 to March 2023 across four tertiary healthcare centers in Peshawar, Pakistan: Khyber Teaching Hospital (KTH), Lady Reading Hospital (LRH), Hayatabad Medical Complex (HMC), and Rehman Medical Institute (RMI). The aim of the study was to evaluate and compare the efficacy of Letrozole (LTZ) and Clomiphene Citrate (CC) in ovulation induction among women diagnosed with Polycystic Ovary Syndrome (PCOS).

Participant Eligibility

Women aged between 20 and 35 years were included if they met the Rotterdam criteria for PCOS. Diagnosis required two of the following three conditions: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on transvaginal ultrasound. Eligible participants had infertility for more than one year (primary or secondary), normal thyroid and prolactin levels, patent fallopian tubes, and partners with normal semen analyses.

Exclusion criteria included the presence of thyroid disorders, hyperprolactinemia, congenital adrenal hyperplasia, adrenal tumors, uterine anomalies, endometriosis, tubal blockage, prior ovarian surgery, or hormonal treatment within the previous three months.

Participant Screening Questionnaire

The table 1 summarizes the data collection instrument used during screening and follow-up.

Table 1: Questionnaire for Participant Screening and Data Collection

Section	Variable	Type of Response	Time of Assessment	Purpose
Demographics	Age (years)	Continuous (exact number)	At enrollment	Eligibility & baseline comparison
	BMI (kg/m²)	Continuous (measured)	At enrollment	Risk factor analysis
	Marital Duration (years)	Continuous	At enrollment	Infertility duration context
	Education level	Categorical (None/Primary/Secondary/Higher)	At enrollment	Socio-demographic profile
Reproductive History	Duration of Infertility (months)	Continuous	At enrollment	Baseline fertility evaluation
	Type of Infertility	Categorical (Primary / Secondary)	At enrollment	Classification of infertility
	Menstrual Regularity	Categorical (Regular / Irregular / Amenorrhea)	At enrollment	PCOS diagnostic component
	Previous pregnancies (if any)	Number (with outcomes)	At enrollment	Past reproductive outcomes
	Use of contraceptives	Yes/No, with type	At enrollment	To rule out confounding factors
PCOS Diagnosis	Oligo/Anovulation	Yes / No	At enrollment	Rotterdam criteria
	Hyperandrogenism (Clinical/Biochemical)	Yes / No (with subtype)	At enrollment	Rotterdam criteria
	Polycystic Ovarian Morphology (TVUS)	Yes / No	Baseline scan	Rotterdam criteria
	Thyroid Function (TSH)	Normal / Abnormal	Baseline lab test	Inclusion/exclusion criteria
	Prolactin Level	Normal / Elevated	Baseline lab test	Inclusion/exclusion criteria
	Fallopian Tube Patency	Yes / No	Pre-study imaging	Eligibility
	Partner's Semen Analysis	Normal / Abnormal	Pre-study	Eligibility
Ovulation Monitoring	TVUS follicular size	Continuous (in mm)	Days 12–16 of each cycle	Ovulation confirmation
	Serum Progesterone (mid-luteal)	>10 ng/mL = ovulation / ≤10 = no ovulation	Mid-luteal of each cycle	Ovulation confirmation
Endometrial Evaluation	Endometrial Thickness (mm)	Continuous	Days 12–16 of each cycle	Implantation potential

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Pregnancy Outcome	β-hCG Result	Positive / Negative	2 weeks post-ovulation	Pregnancy detection
	Ultrasound Gestational Confirmation	Intrauterine / None	5–6 weeks post-ovulation	Clinical pregnancy
Treatment-Related Effects	Side Effects Reported	Categorical (Checklist)	Throughout study	Safety and tolerability monitoring
	Specific Side Effects (e.g., hot flashes, nausea, etc.)	Yes / No + Severity Scale (mild/moderate/severe)	Ongoing	Comparative safety profile
Treatment Details	Dose Used per Cycle (Letrozole or CC)	2.5/5/7.5 mg or 50/100/150 mg	Each cycle	Correlation with outcomes
	Treatment adherence	Full / Partial / Missed	Each cycle	Protocol fidelity

Sample Size and Randomization

Sample size was calculated to detect a 20% difference in ovulation rate, with 95% confidence and 80% power. A minimum of 158 participants were required, 79 in each group. Eligible women were consecutively enrolled and randomized using computer-generated block randomization (block size of four). Allocation was concealed through sequentially numbered, opaque, sealed envelopes prepared by an independent statistician.

Intervention Protocol

Group A (Letrozole) received Letrozole 2.5 mg orally on cycle days 3–7. In the absence of ovulation, doses were increased to 5 mg in the second and 7.5 mg in the third cycle. Group B (Clomiphene Citrate) received 50 mg orally on the same cycle days, with step-ups to 100 mg and 150 mg in cycles two and three respectively, following the same escalation schedule as Letrozole. Treatment was continued for a maximum of three cycles or until pregnancy was confirmed.

Monitoring and Outcome Measures

Follicular development and endometrial thickness were monitored via transvaginal ultrasound on cycle days 12 to 16. Ovulation was confirmed by the presence of a dominant follicle (≥18 mm) and/or serum progesterone >10 ng/mL in the mid-luteal phase. Pregnancy was confirmed by a positive serum β-hCG test and intrauterine gestation on ultrasound.

Primary outcome was ovulation rate per group. Secondary outcomes included endometrial thickness, clinical pregnancy rate, and treatment-related side effects. Adverse effects were monitored and recorded using standardized forms. Independent assessors blinded to treatment group performed ultrasound evaluations.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were reported as means ± standard deviations, while categorical variables were presented as frequencies and percentages. Chi-square or Fisher's exact tests were used for categorical variables. Independent samples t-test and Mann–Whitney U test compared continuous variables based on data normality. Repeated measures of endometrial thickness were analyzed using paired t-tests and repeated-measures ANOVA (Greenhouse–Geisser correction). Logistic regression identified predictors of ovulation and pregnancy, reported as adjusted odds ratios (OR) with 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of Khyber Medical University, Peshawar. Written informed consent was obtained from all participants after explaining study goals, risks, and benefits. Data confidentiality and participant autonomy were ensured throughout.

Results

A research trial included 158 PCOS patients who received treatment between the Letrozole group comprising 79 participants and the Clomiphene Citrate group with 79 members. All subjects finished the research without abandoning it. The Letrozole treatment group consisted of women whose mean age was 28.5 ± 4.2 years while the Clomiphene Citrate treatment group had an average age of 28.6 ± 4.1 years ($p = 0.821$). BMI did not differ significantly between

groups as the Letrozole group possessed a mean of 27.3 ± 4.6 kg/m² while the Clomiphene Citrate group had a mean of 27.2 ± 4.3 kg/m² (p = 0.761). The groups' infertility durations were identical, with the Letrozole group having 21.3 ± 5.7 months and the Clomiphene Citrate group 20.9 ± 5.3 months (p = 0.651). Regarding oligo/anovulation, 69.6% of participants in the Letrozole group and 68.4% in the Clomiphene Citrate group exhibited this condition (p = 0.821). The types of infertility and the presence of polycystic ovarian morphology were also comparable between the two groups. These findings show that baseline attributes did not change much. Table 2 displays the baseline demographics and features of both groups. At baseline, there were no notable variations among the groups (all p-values >0.05).

Table 2: Baseline Demographic Characteristics

Characteristic	Letrozole Group (n=79)	Clomiphene Citrate Group (n=79)	p-value
Age (years)	28.5 ± 4.2	28.6 ± 4.1	0.821
Body Mass Index (BMI) (kg/m²)	27.3 ± 4.6	27.2 ± 4.3	0.761
Duration of Infertility (months)	21.3 ± 5.7	20.9 ± 5.3	0.651
Oligo/anovulation (%)	55 (69.6%)	54 (68.4%)	0.821
Primary Infertility (%)	50 (63.3%)	51 (64.6%)	0.876
Secondary Infertility (%)	29 (36.7%)	28 (35.4%)	0.876
Polycystic Ovarian Morphology (%)	75 (94.9%)	76 (96.2%)	0.734

**P-value <0.05: significant*

The study's main finding was the ovulation rate, which was considerably greater in the Letrozole group than in the Clomiphene Citrate group. Ovulation took place in 68 out of 79 women (86.1%) receiving Letrozole, whereas only 53 out of 79 women (67.1%) in the Clomiphene Citrate group achieved ovulation. This difference was statistically significant (p = 0.002), indicating a superior ovulation-inducing effect of Letrozole. Overall, 121 out of 158 participants (76.6%) ovulated during the study period. These results imply that letrozole may induce ovulation in women receiving infertility treatment more successfully than clomiphene citrate. The findings add credence to the increasing amount of data supporting letrozole as a first-line treatment for ovulation induction (as illustrated in figure 1).

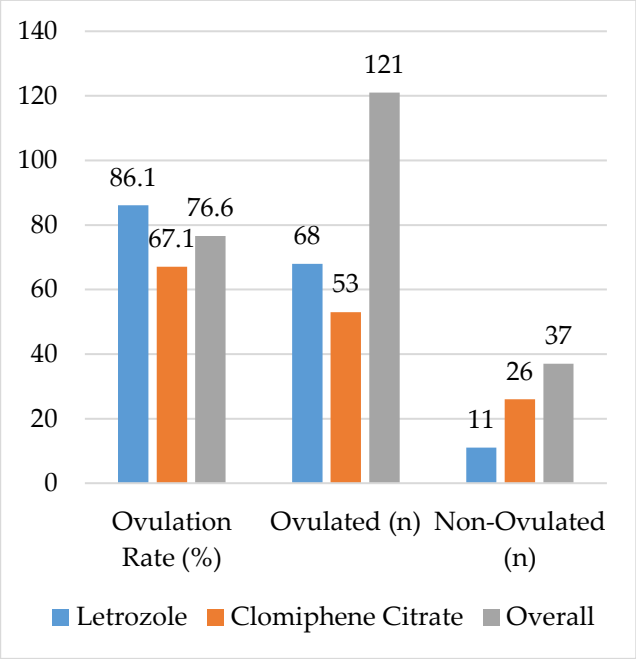

Figure 1: Ovulation Rate Comparison between Groups

Between cycle days 12 and 16, the thickness of endometrium was measured, and the two treatment groups' results showed a substantial difference. Compared to the Clomiphene Citrate group, the Letrozole group's average thickness of endometrium was noticeably greater (9.2 ± 1.4 mm vs. 8.4 ± 1.2 mm, p = 0.003). Both groups exhibited progressive increases in endometrial thickness from Cycle 1 to Cycle 3; however, the Letrozole group demonstrated a more pronounced improvement. Specifically, endometrial thickness in the Letrozole group increased from 8.1 ± 1.2 mm in Cycle 1 to 9.2 ± 1.4 mm in Cycle 3, whereas in the Clomiphene Citrate group, it rose from 7.8 ± 1.1 mm to 8.4 ± 1.2 mm (p = 0.013). According to these results, letrozole might have a greater positive impact on endometrial growth, which could positively impact implantation and pregnancy outcomes as shown in table 3.

Table 3: Endometrial Thickness Comparison

Group	Endometrial Thickness (mm)			p-value
	Cycle 1	Cycle 2	Cycle 3	
Letrozole	8.1 ± 1.2	8.7 ± 1.3	9.2 ± 1.4	0.003
Clomiphene Citrate	7.8 ± 1.1	8.1 ± 1.2	8.4 ± 1.2	0.013
Overall	8.0 ± 1.2	8.4 ± 1.2	8.8 ± 1.3	-

**P-value <0.05: significant*

The clinical pregnancy rate served as the secondary outcome of the study, with results indicating an increased rate of pregnancy in the group taking letrozole as opposed to the group taking clomiphene citrate. Specifically, 31 out of 79 women (39.2%) in the Letrozole group became pregnant, whereas 24 out of 79 women (30.4%) in the Clomiphene group achieved pregnancy. Though this variation did not achieve statistical importance (p = 0.141), the trend favored Letrozole in terms of pregnancy outcomes. Overall, 55 out of 158 participants (34.8%) became pregnant during the study period. These results suggest a potential clinical advantage of Letrozole over Clomiphene Citrate, warranting further investigation with larger sample sizes to confirm its efficacy in enhancing pregnancy rates. Although the 9% absolute increase in pregnancies did not achieve conventional statistical significance, it equates to one additional pregnancy for every 11 women treated with LTZ (number needed to treat = 11), a figure that may be clinically meaningful for couples facing limited treatment cycles or financial constraints (Figure 2).

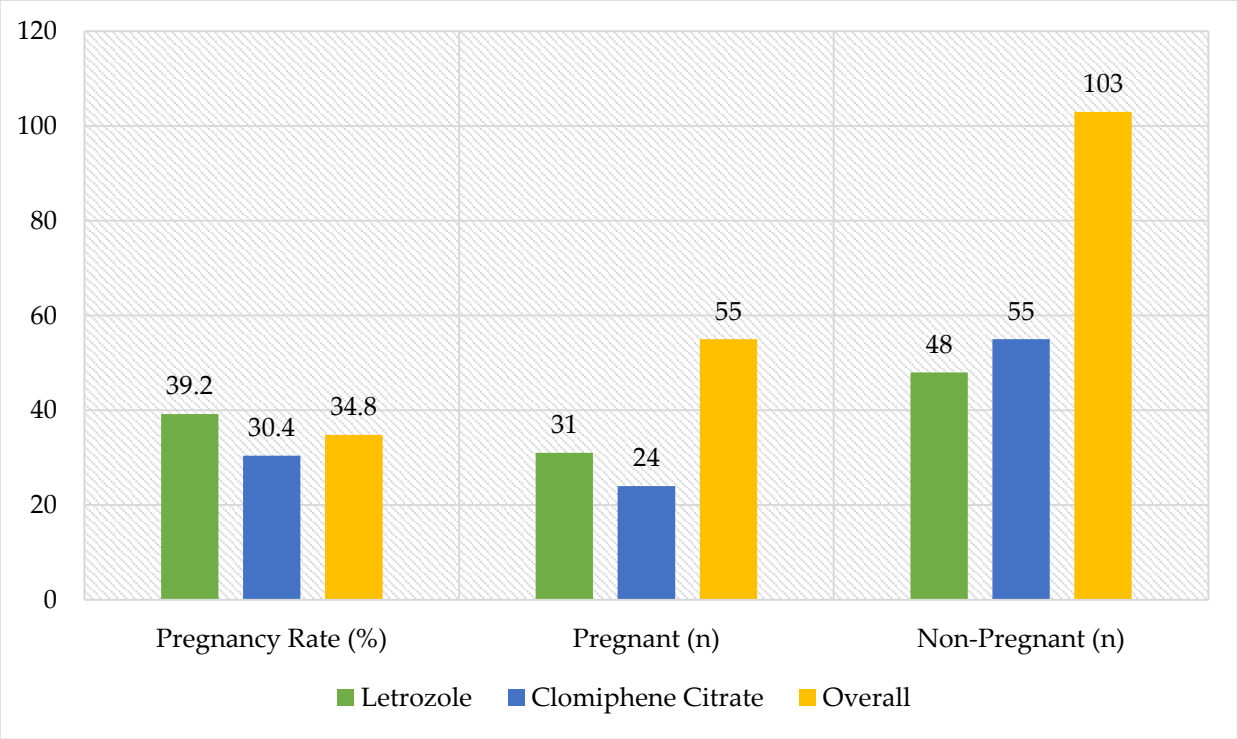

Figure 2: Pregnancy Rate Comparison between Groups

Adverse effects were recorded in both treatment groups, with the most commonly reported symptoms being hot flashes, abdominal discomfort, mood swings, and nausea. In the Letrozole group, 19 out of 79 women (24.1%) experienced hot flashes, compared to 21 out of 79 women (26.6%) in the Clomiphene Citrate group (p = 0.622). Abdominal discomfort was reported by 9 women (11.4%) in the Letrozole group and 8 women (10.1%) in the Clomiphene group (p = 0.732). Mood swings were noted in 7 women (8.9%) in the Letrozole group versus 6 women (7.6%) in the Clomiphene group (p = 0.821), while nausea occurred in 3 women (3.8%) and 4 women (5.1%) in the Letrozole and Clomiphene groups, respectively (p = 0.732). The incidence of negative effects did not differ significantly among both groups. Additionally, 44 women (55.7%) in each group reported no side effects (table 4). Both treatments were well tolerated. The most commonly reported side effects were hot flashes, abdominal discomfort, mood swings, and nausea. No significant differences were found in the incidence of any side effects between the two groups.

Table 4: Adverse Effects Comparison between Groups

Side Effect	Letrozole Group (n = 79)	Percentage	Clomiphene Group (n = 79)	Percentage	p-value
Hot Flashes	19	24.1	21	26.6	0.622
Abdominal Discomfort	9	11.4	8	10.1	0.732
Mood Swings	7	8.9	6	7.6	0.821
Nausea	3	3.8	4	5.1	0.732
No Side Effects	44	55.7	44	55.7	—

**P-value <0.05: significant*

Discussion

The clinical pregnancy rate served as the secondary outcome of the study, with results indicating an increased rate of pregnancy in the group taking letrozole as opposed to the group taking clomiphene citrate. Specifically, 31 out of 79 women (39.2%) in the Letrozole group became pregnant, whereas 24 out of 79 women (30.4%) in the Clomiphene group achieved pregnancy. Though this variation did not achieve statistical importance (p = 0.141), the trend favored Letrozole in terms of pregnancy outcomes.

Overall, 55 out of 158 participants (34.8%) became pregnant during the study period. These results suggest a potential clinical advantage of Letrozole over Clomiphene Citrate, warranting further investigation with larger sample sizes to confirm its efficacy in enhancing pregnancy rates. Although the 9% absolute increase in pregnancies did not achieve conventional statistical significance, it equates to one additional pregnancy for every 11 women treated with LTZ (number needed to treat = 11), a figure that may be clinically meaningful for couples facing limited treatment cycles or financial constraints.

This research confirms that Letrozole creates more effective ovulation outcomes than Clomiphene Citrate for women with PCOS [13]. Letrozole demonstrated a superior ovulation-stimulating effect on PCOS patients according to results of other researches especially when patients failed to respond to Clomiphene Citrate therapy [14]. The reduction of estrogen through aromatase inhibitor activity in Letrozole treatment leads to higher secretion of follicle-stimulating hormone (FSH) essential for ovulation [15].

Numerous studies confirm that endometrial thickness reaches higher levels when women take Letrozole instead of Clomiphene Citrate including our research [16]. The relation of thicker endometrium to improved implantation results should be noted since it represents a beneficial condition for pregnancy success. Use of Clomiphene Citrate leads to a distorted endometrium because of its anti-estrogenic nature that potentially harms implantation success and pregnancy probabilities [17].

The research data showed that Letrozole provided superior pregnancy results, but these differences failed to achieve statistical meaning. This pregnancy rate finding matches research that shows improved results with Letrozole treatment while the differences in outcomes demonstrate multiple influencing factors such as ovarian reserve as well as sperm quality together with hormonal elements [18].

Research investigations demonstrate Letrozole can improve ovulation and endometrial thickness, but such enhancements fail to demonstrate substantial variation in pregnancy results as compared to Clomiphene Citrate treatment [19]. The side effects of these drugs are equally common and consist of hot flashes, abdominal discomfort and mood swings thereby supporting earlier research that demonstrates Letrozole maintains more advantageous side effects compared to Clomiphene Citrate [20]. The safety findings of this study strengthen the evidence supporting Letrozole since Clomiphene Citrate risked ovarian hyperstimulation syndrome (OHSS), although not reported in the present study [21].

In addition to clinical outcomes, treatment accessibility is an important consideration in Pakistan's healthcare system. Letrozole is often costlier and less readily available than clomiphene citrate in many public-sector pharmacies. This disparity may limit its widespread adoption despite better clinical outcomes. Therefore, health policy makers must weigh both efficacy and affordability when updating fertility treatment protocols in resource-constrained settings.

Limitations and Future Suggestions

This study has several limitations. The study size was sufficient yet insufficient to reveal meaningful changes in pregnancy rates because PCOS women have volatile reproductive results. The analysis

excluded important factors affecting pregnancy outcomes including sperm quality along with ovarian reserve and lifestyle element. The study had brief follow-up duration which prevented an evaluation of live birth rates together with both maternal and fetal health outcomes.

Future investigations should execute research involving bigger multicenter research combined with extended follow-up durations to examine sustained pregnancy results. Additional studies investigating how Letrozole performs against other ovulation medications or dual treatment methods may improve understanding of the best therapies for PCOS analogs. It is essential to measure the cost-effectiveness of Letrozole against Clomiphene Citrate since it matters significantly in low-resource environments.

Conclusion

Letrozole proves superior over Clomiphene Citrate when intended for ovulation stimulation in women with PCOS since it produces higher ovulation rates alongside enhanced endometrial thickness measurement. The pregnancy rate remained higher for patients who received Letrozole but the difference between groups did not achieve statistical significance. The drugs produced comparable safety outcomes as they resulted in similar negative effects. These findings suggest LTZ could confer a modest but potentially important clinical advantage in pregnancy achievement, meriting confirmation in larger trials powered for live-birth endpoints. Additional investigation involving larger participant numbers and expanded observation times must be conducted to examine extended pregnancy results as well as enhance treatment methods for PCOS patients.

Ethical Considerations

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed written consent was obtained from all participants prior to enrollment. Ethical approval was obtained from the institutional ethics committee of the participating hospitals.

Authors' contributions

MM: Conception and design of the study, data collection, manuscript drafting, and final approval.
GS: Literature review, methodology development, critical revision of the manuscript, and final approval.

SJ: Data analysis, interpretation of results, manuscript drafting and revision, and final approval.

HA: Data acquisition, assistance in statistical analysis, manuscript revision, and final approval.

AQ: Data collection, proofreading and editing of the manuscript, and final approval.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declared no conflict of interest.

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