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Comparative Analysis of Letrozole vs. Clomiphene Citrate in Women with PCOS Undergoing Ovulation Induction

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ABSTRACT

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

Methods: A prospective comparative study was conducted at Department of Gynaecology and obstetrics Dr Ziauddin university Karachi from February 2023 to February 2024. A total of 71 women with PCOS were enrolled and randomly assigned to two groups: Group A (n=36) received Letrozole, while Group B (n=35) received Clomiphene Citrate. Patients were monitored with transvaginal ultrasonography for follicular growth, endometrial thickness, and ovulation. Outcomes assessed included ovulation rate, endometrial response, biochemical pregnancy, clinical pregnancy, live birth, and adverse effects. Data were analyzed using SPSS version 26, with $p<0.05$ considered significant.

Results: Baseline demographic and hormonal profiles were similar across groups. Women treated with Letrozole developed a thicker endometrium than those receiving Clomiphene (8.7 ± 1.2 mm versus 7.3 ± 1.4 mm, p=0.001). Clomiphene induced a higher mean number of mature follicles (2.4 ± 0.8 vs. 1.8 ± 0.6, p=0.004). Ovulation and pregnancy rates were higher with Letrozole, though not statistically significant. Adverse effects such as ovarian cyst formation and hot flushes were more common in the Clomiphene group.

Conclusion: Letrozole demonstrated superior endometrial development, comparable follicular response, and a trend toward better pregnancy outcomes with fewer adverse 'effects compared to Clomiphene Citrate'. These findings support the use of Letrozole as a preferred first-line agent for ovulation induction in women with PCOS.

Keywords: *Polycystic ovary syndrome, Letrozole, Clomiphene Citrate, Ovulation induction, Infertility, Pregnancy outcomes*

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with a global prevalence estimated between 6–20% depending on diagnostic criteria. It is characterized by 'chronic anovulation, hyperandrogenism, and polycystic ovarian morphology' frequently resulting in infertility. In Pakistan and other South Asian countries, PCOS has emerged as a significant public health concern, with studies indicating rising trends linked to lifestyle changes, obesity, and genetic predisposition [1-3].

Ovulation induction remains the cornerstone of infertility management in women with PCOS. 'Clomiphene Citrate has long been the first-line agent' due to its low cost, oral administration, and proven efficacy. However, its anti-estrogenic effect on the endometrium and cervical mucus, along with the risk of multiple follicular development, can reduce implantation potential and increase adverse outcomes. Moreover, a considerable proportion of women develop Clomiphene resistance, limiting its effectiveness [4-6].

In contrast, Letrozole, an aromatase inhibitor, has gained increasing popularity as an alternative ovulation induction agent. By reducing estrogen synthesis, 'it releases the hypothalamic-pituitary axis from negative feedback' resulting in increased follicle-stimulating hormone (FSH) secretion. Importantly, Letrozole does not exert anti-estrogenic effects on the endometrium, which may enhance receptivity and implantation. Several international studies, including the large multicenter PPCOS II trial, demonstrated higher ovulation and live birth rates with Letrozole compared to Clomiphene Citrate. Regional studies have echoed similar findings, suggesting its potential as the preferred first-line therapy for PCOS-related infertility [7-9].

Despite this growing evidence, many gynecologists in low- and middle-income countries, including Pakistan, continue to prescribe Clomiphene as the initial treatment due to its widespread availability and long history of use. This underscores the need for local comparative studies to generate evidence relevant to the regional population.

The present study was therefore designed 'to compare the efficacy and safety of Letrozole versus Clomiphene Citrate in women with PCOS undergoing ovulation induction'. By assessing ovulation rates, pregnancy outcomes, and treatment-related side effects, this study aims to contribute locally generated data that can guide clinical decision-making and improve reproductive outcomes for women with PCOS.

2. METHODOLOGY

This was a prospective comparative study conducted at Department of Gynaecology and obstetrics Dr Ziauddin university Karachi from February 2023 to February 2024. A total of 71 women diagnosed with polycystic ovary syndrome (PCOS) were enrolled. The study compared the efficacy of 'Letrozole and Clomiphene Citrate for ovulation induction in women seeking treatment for infertility'.

The final sample size consisted of 71 participants, divided into two groups: 36 received Letrozole and 35 received Clomiphene Citrate. Participants were recruited through consecutive non-probability sampling based on inclusion and exclusion criteria.

Inclusion Criteria

- Women aged 20–35 years.
- Diagnosed with PCOS according to the Rotterdam criteria (presence of at least two of the following: 'oligo/anovulation, clinical/biochemical hyperandrogenism, polycystic ovarian morphology on ultrasound)'.
- History of infertility for at least one year.
- Normal uterine cavity and bilateral tubal patency confirmed by hysterosalpingography or laparoscopy.
- Male partner with normal semen parameters as per WHO 2021 guidelines.

Exclusion Criteria

- Women with other causes of infertility such as endometriosis, uterine anomalies, or tubal blockage.
- Patients with thyroid dysfunction, hyperprolactinemia, or uncontrolled diabetes mellitus.
- Women with previous ovarian surgery or known resistance to ovulation induction drugs.
- Contraindications to Letrozole or Clomiphene Citrate therapy.

Participants were randomly assigned into two groups using a computer-generated list:

- 'Group A (Letrozole): Received 2.5 mg Letrozole orally daily from cycle day 3 to 7'. Dose was increased to 5 mg in subsequent cycles if no follicular development was observed.
- Group B (Clomiphene Citrate): Received 50 mg Clomiphene Citrate orally daily from cycle day 3 to 7. Dose was escalated to 100 mg in subsequent cycles if ovulation did not occur.

Baseline transvaginal ultrasonography was performed 'on day 2 of the cycle to exclude ovarian cysts and assess antral follicle count'. Follicular growth was monitored by ultrasound starting from cycle day 10, repeated every 2–3 days until the leading follicle reached ≥18 mm. Endometrial thickness was also measured on the day of human chorionic gonadotropin (hCG) trigger.

When at least one follicle reached ≥18 mm, 5,000 IU of hCG was administered intramuscularly to trigger ovulation. Patients were advised timed intercourse within 36 hours after hCG injection.

The following parameters were assessed and compared between the two groups:

- Ovulation rate (confirmed by ultrasound).
- Number of mature follicles and maximum follicle diameter.
- Endometrial thickness on the day of hCG administration.
- Biochemical pregnancy rate (serum β-hCG positive two weeks after ovulation).
- Clinical pregnancy rate (confirmed by the presence of a gestational sac with fetal cardiac activity on ultrasound).
- Adverse effects such as ovarian cyst formation, hot flushes, or ovarian hyperstimulation.

Data were analyzed using SPSS version 26. Continuous variables such as age, BMI, duration of infertility, endometrial thickness, and number of follicles were expressed as mean ± standard deviation and compared between groups using an independent t-test. Outcomes of a categorical nature, including 'ovulation rate, pregnancy-related measures, and adverse reactions' were reported as frequency and proportion. Statistical comparison between groups was performed using either the 'Chi-square test or Fisher's exact test' with significance defined at $p<0.05$

3. RESULTS

The study included 71 women with PCOS, divided into two groups: 36 received Letrozole and 35 received Clomiphene Citrate. The mean age of participants was comparable between the two groups (27.4 ± 3.2 years in Letrozole vs. 28.1 ± 3.6 years in Clomiphene, p=0.41). Similarly, the mean BMI did not differ significantly (26.8 ± 4.1 vs. 27.2 ± 4.5, p=0.63). The average duration of infertility was slightly longer in the Clomiphene group but the difference was not statistically significant (p=0.55). The distribution of primary and secondary infertility, as well as menstrual irregularities, showed no significant difference. Clinical features such as hirsutism and acne were also comparable between the two groups (p>0.05). Baseline hormonal values including FSH, LH, LH/FSH ratio, AMH, and testosterone levels were well matched, indicating homogeneity of the study population.

Table 1: Baseline Demographic and Clinical Characteristics of Participants

Variable	Letrozole Group (n=36)	Clomiphene Group (n=35)	p-value
Mean Age (years)	27.4 ± 3.2	28.1 ± 3.6	0.41
BMI (kg/m²)	26.8 ± 4.1	27.2 ± 4.5	0.63
Duration of Infertility (years)	3.1 ± 1.5	3.3 ± 1.7	0.55
Type of Infertility			
• Primary	26 (72.2%)	25 (71.4%)	0.94
• Secondary	10 (27.8%)	10 (28.6%)	
Menstrual Pattern			
• Oligomenorrhea	28 (77.8%)	27 (77.1%)	0.92
• Amenorrhea	8 (22.2%)	8 (22.9%)	
Clinical Features			
• Hirsutism (FG >8)	22 (61.1%)	20 (57.1%)	0.73
• Acne	15 (41.7%)	16 (45.7%)	0.77
Baseline Hormonal Levels			
FSH (mIU/mL)	6.1 ± 1.8	6.3 ± 1.7	0.68
LH (mIU/mL)	10.5 ± 3.6	10.8 ± 3.9	0.71
LH/FSH Ratio	1.7 ± 0.6	1.8 ± 0.7	0.49

AMH (ng/mL)	6.2 ± 1.9	6.4 ± 2.1	0.66
Serum Testosterone (ng/dL)	54.1 ± 15.3	56.4 ± 16.1	0.58

Analysis of ovarian response demonstrated that endometrial thickness 'on the day of hCG administration was significantly greater in the Letrozole group compared to the Clomiphene group' (8.7 ± 1.2 mm vs. 7.3 ± 1.4 mm, p=0.001). Conversely, the number of mature follicles was higher in the Clomiphene group (2.4 ± 0.8 vs. 1.8 ± 0.6, p=0.004). The maximum follicle diameter was similar between groups (p=0.38). Ovulation occurred in 77.8% of women on Letrozole and 65.7% on 'Clomiphene, though the difference was not statistically significant (p=0.21)'. Cycle cancellation 'rates were slightly higher in the Clomiphene group but not significane (p=0.42)'.

Table 2: Ovarian Response and Cycle Monitoring Parameters

Variable	Letrozole Group (n=36)	Clomiphene Group (n=35)	p-value
Endometrial Thickness on hCG day (mm)	8.7 ± 1.2	7.3 ± 1.4	0.001*
Number of Mature Follicles (≥18 mm)	1.8 ± 0.6	2.4 ± 0.8	0.004*
Maximum Follicle Diameter (mm)	19.6 ± 2.1	20.1 ± 2.3	0.38
Ovulation Rate	28 (77.8%)	23 (65.7%)	0.21
Cycle Cancellation Rate	3 (8.3%)	5 (14.3%)	0.42

(*p < 0.05 significant)

In terms of pregnancy outcomes, the Letrozole group showed a higher biochemical pregnancy rate (33.3% vs. 22.9%) and clinical pregnancy rate (27.8% vs. 20.0%) compared to the Clomiphene group, although these differences were not statistically significant (p>0.05). Multiple pregnancies occurred in both groups but remained low, and miscarriage rates were comparable (5.6% vs. 8.6%). The live birth rate favored Letrozole (25.0% vs. 17.1%) but again without statistical significance. Adverse effects were more commonly observed with Clomiphene, including cyst formation (14.3% vs. 5.6%) and hot flushes (11.4% vs. 2.8%), though these differences did not reach statistical significance. Overall, Letrozole demonstrated a trend toward better pregnancy outcomes and fewer side effects compared to Clomiphene.

Table 3: Pregnancy and Treatment Outcomes

Outcome	Letrozole Group (n=36)	Clomiphene Group (n=35)	p-value
Biochemical Pregnancy Rate	12 (33.3%)	8 (22.9%)	0.32
Clinical Pregnancy Rate	10 (27.8%)	7 (20.0%)	0.45
Multiple Pregnancy Rate	1 (2.8%)	2 (5.7%)	0.56
Miscarriage Rate	2 (5.6%)	3 (8.6%)	0.64
Live Birth Rate (if followed)	9 (25.0%)	6 (17.1%)	0.39
Adverse Effects			
• Ovarian Cyst Formation	2 (5.6%)	5 (14.3%)	0.19
• Hot Flushes	1 (2.8%)	4 (11.4%)	0.14

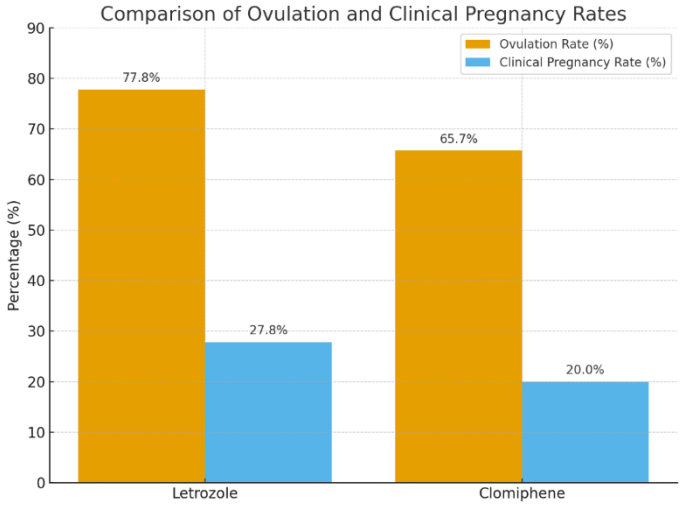

Figure 1: Bar chart comparing the ovulation and clinical pregnancy rates between Letrozole and Clomiphene groups.

4. DISCUSSION

The present study compared the efficacy of Letrozole and Clomiphene Citrate in women with PCOS undergoing ovulation induction. Although baseline characteristics such as age, BMI, duration of infertility, and hormonal parameters were similar between the groups, differences emerged in endometrial development, follicular response, and pregnancy outcomes.

Our findings revealed that Letrozole was associated with a significantly greater endometrial thickness compared to Clomiphene. This observation is consistent with the studies reported that Letrozole exerts a more favorable effect on the endometrium due to the absence of anti-estrogenic activity. In contrast, Clomiphene often results in endometrial thinning, which may impair implantation despite adequate follicular response [10-12].

The Clomiphene group in our study produced a higher number of mature follicles, which aligns with findings from studies [13-15] However, the clinical relevance of this observation remains debatable, as multiple follicle development carries a risk of multiple pregnancy without necessarily improving overall live birth rates. In our results, although the Clomiphene group showed slightly more multiple gestations, these were few in number and not statistically significant.

'Ovulation rates were higher with Letrozole compared to Clomiphene, although the difference did not reach statistical significance'. This trend mirrors the results of the PPCOS II trial, a large multicenter randomized study, which demonstrated significantly higher ovulation and 'live birth rates with Letrozole'. Similarly, studies highlighted Letrozole as the superior first-line agent for ovulation induction in PCOS due to both improved efficacy and a better safety profile. [16-18]

In terms of pregnancy outcomes, our study showed higher biochemical and 'clinical pregnancy rates with Letrozole compared to Clomiphene, though these differences were not statistically significant'. This finding is comparable with **studies** Cochrane review concluded that Letrozole improves live birth and clinical pregnancy rates in PCOS women compared to Clomiphene. Regional data also support these trends: a study conducted in Pakistan reported that Letrozole achieved higher ovulation and pregnancy rates than Clomiphene, reinforcing the global evidence base [19].

Adverse effects were more common in the Clomiphene group, particularly ovarian cyst formation and hot flushes. This is in line with previous studies, who emphasized the better tolerability of Letrozole. Importantly, the incidence of ovarian hyperstimulation was low in both groups, confirming the safety of both drugs when monitored appropriately [20].

Taken together, our findings suggest that while both agents are effective for ovulation induction, Letrozole appears to offer a more favorable endometrial profile and a trend toward better pregnancy outcomes with fewer side effects. The relatively small sample size in our study may have limited the statistical power to detect significant differences in pregnancy rates. Nevertheless, the observed trends are consistent with larger international trials and strengthen the case for adopting 'Letrozole as the first-line treatment for women with PCOS'.

5. CONCLUSION

This study demonstrated that Letrozole provides better endometrial development and comparable or higher 'pregnancy rates compared to Clomiphene Citrate in women with PCOS undergoing ovulation induction'. Although Clomiphene produced more mature follicles, this did not translate into superior pregnancy outcomes. 'Adverse effects were more frequently noted with Clomiphene, whereas Letrozole' was better tolerated. Based on our results and existing evidence, Letrozole may be considered the more effective and safer first-line ovulation induction agent in women with PCOS. Larger multicenter trials

in local populations are recommended to further validate these findings and establish national treatment guidelines.

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