



## Original Article



## Impact of Letrozole on Mature Follicle Rate in Treatment of Subfertility Due to Polycystic Ovarian Syndrome

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## ABSTRACT

Letrozole was an aromatase inhibitor that has gained prominence as an alternative to the clomiphene citrate for ovulation induction in females with Polycystic Ovarian Syndrome (PCOS). **Objective:** To assess the frequency of mature follicle rate as a result of letrozole treatment in subfertility due to PCOS. **Methods:** This interventional study was performed at Obstetrics and Gynecology Department, Combined Military Hospital, Multan, over a period of 6 months, from March 1, 2023 to September 1, 2023. The study included 322 cases aged between 20–40 years, who reported infertility for longer than a year, had Body Mass Index (BMI) <28, and had subfertility due to PCOS. All study participants were subjected to letrozole treatment. Development of mature follicles was observed utilizing transvaginal ultrasound starting from the 10<sup>th</sup> day of treatment. **Results:** The mean age of patients was  $32.82 \pm 4.30$  years. The mean weight was  $61.74 \pm 7.35$  kg, whereas the mean height was  $1.61 \pm 0.069$  m. The mean BMI was  $23.68 \pm 2.96$  kg/m<sup>2</sup>. Among the participants, 161 (50.0%) patients had primary infertility, and 161 (50.0%) had secondary infertility. After receiving letrozole treatment, 237 (73.6%) patients had mature follicles on ultrasonography. **Conclusions:** Letrozole seems to improve the rate of follicle maturation in women with subfertility due to PCOS, thereby increasing the likelihood of pregnancy. Based on these findings, letrozole can be regarded as a suitable alternative to first-line therapies such as clomiphene citrate, providing favorable outcomes and minimal side effects, specifically in patients with clomiphene citrate resistance.

## INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most frequently occurring endocrine dysfunction in females, affecting approximately 4–18% of reproductive age women all over the world [1]. The prevalence of PCOS is higher among Pakistani women (33.3%) compared to Western women (20–25%) [2, 3]. It is identified as irregular menstrual cycle, manifestation of overabundance of androgen such as acne and hirsutism, and the presence of multiple small cysts in the ovaries, as seen on USG [4]. Although it is one of the many paramount reasons of infertility in women of reproductive age, its cause is still undetermined and its management is complex [5, 6]. Recent studies have demonstrated that PCOS is linked with anovulatory

infertility and the induction of ovulation is the primary goal in managing PCOS-induced infertility. Weight reduction, lifestyle modifications, and several pharmacological agents such as metformin and clomiphene citrate are various strategies for managing PCOS [7]. Aromatase inhibitors, specifically letrozole, were introduced by Mitwally and Casper in 2001 for the induction of ovulation [8]. It is a potential non-steroidal agent that functions by reducing the conversion of androstenedione and testosterone into estrogen [9]. By diminishing the body levels of estrogen, letrozole alleviates the negative feedback on the hypothalamus and pituitary gland. This causes raised Follicle-Stimulating Hormone (FSH) and



Luteinizing Hormone (LH) levels, which stimulate the ovarian follicle development [10]. Letrozole exhibits a mono-follicular response and does not cause adverse effects on endometrium and mucosa of cervix, due to its lack of estrogen receptor blockage. Also, it is cleared from circulation more quickly due to its shorter half-life (2 days) [11]. Compared to other similar drugs, it has a lower risk of multiple pregnancies, ovarian hyperstimulation syndrome, and congenital fetal malformations [12, 13]. The main side effects of this drug are headache, gastro-intestinal disturbances, joint ache, flushing, and sweating [14]. Due to presence of evidence regarding safety and efficacy of letrozole, it has been approved by the US Food and Drug Administration for first line treatment [15, 16]. Several studies have reported a varied impact of letrozole in treating subfertility in women with PCOS. A study reported that mature follicles rate ( $\geq 17$  mm in size) was 38% in patients receiving letrozole treatment [6]. Another systematic review reported that the possibility of ovulation was much higher in letrozole [17]. Another study reported the ovulation rate was 86.7% following the administration of letrozole [18].

Given the dearth of local evidence and the contrasting results from global data regarding the number of mature follicles, the rationale of this study was to determine the frequency of mature follicles in patients receiving letrozole for the treatment of subfertility due to PCOS. If this study finds a higher number of mature follicles, it could possibly result in considering letrozole as a first-line therapy in the future. Moreover, letrozole is a safer drug and can effectively substitute the first-line drugs for ovulation induction in patients with PCOS.

Thereby, it could be regarded as a feasible first-line treatment option for inducing ovulation in these cases.

## METHODS

The interventional study was carried out at Obstetrics and Gynecology department, Combined Military Hospital, Multan, for 6 months from 1<sup>st</sup> march to 1<sup>st</sup> September 2023. Sample size of 322 was measured utilizing 95% confidence level, 5% margin of error and expected percentage of mature follicles in the group getting letrozole as 70.21% [19]. Consecutive sampling technique was utilized to gather the data. Patients aged between 20–40 years, reporting infertility for longer than a year, having body mass index  $< 28$  kg/m<sup>2</sup>, and having subfertility owing to PCOS (absence of ovulation, symptoms of increase in androgen in the blood such as hirsutism and acne, and the raised levels of testosterone in the blood) were included in the study. Patients having tubal patency on hysterosalpingography, abnormal follicle stimulating hormone, luteinizing hormone, prolactin, progesterone, estrogen, and testosterone levels or patients whose husbands had abnormal semen analysis report were excluded from the study. The study proposal was submitted to the

institutional ethical committee of Combined Military Hospital, Multan for review and approval. The Committee examined the adherence of the study to ethical standards, including participant safety, privacy, and the risk-benefit ratio and the approval was granted on 1<sup>st</sup> Jan, 2023 with the reference number (ERC No. 24/2024). Informed consent was obtained from all patients before including them in the study. Detailed information regarding the objectives, procedures, possible risks, and benefits of the study was given to patients through a written consent form. It was designed to ensure that patients had ample and appropriate information to make an informed decision about their inclusion in the study. Data were then taken from each patient meeting the inclusion criteria. All cases were diagnosed for subfertility and PCOS using Rotterdam criteria [20]. Initial dose of 2.5 mg letrozole was given to all patients, and then the dose was escalated up to 5 mg per day for 5 consecutive days beginning from the day 3 of the menstruation, as recommended in the literature [9, 18]. Each woman continued to receive metformin 500 mg thrice a day, as recommended in the previous studies [21]. Development of mature follicles was observed utilizing transvaginal ultrasound starting from the 10<sup>th</sup> day of treatment. A subcutaneous injection of 10,000 IU of Human Chorionic Gonadotropin (hCG) was given to activate ovulation as soon as at least one mature follicle having a mean diameter  $\geq 18$  mm was seen on TVUS. All data was collected by researcher herself. All data was entered and analyzed utilizing Statistical Package for Social Sciences (SPSS) version 23.0. Quantitative data such as age, weight, height, and body mass index were presented as mean  $\pm$  standard deviation. Categorical data like type of infertility and number of mature follicles were presented as frequencies and percentages. Chi-square test was utilized to compare the number of mature follicles following letrozole treatment with respect to age, body mass index and type of infertility.

## RESULTS

A total of 322 patients were included in the study. Baseline characteristics were explained in table 1. Mean age of patients was  $32.82 \pm 4.30$  years, with a range of 20 years. Mean weight of the patients was  $61.74 \pm 7.35$  kg whereas the mean height was  $1.61 \pm 0.069$  m. Mean BMI was  $23.68 \pm 2.96$  kg/m<sup>2</sup>. Among these patients, 161(50.0%) patients had primary infertility and 161(50.0%) had secondary infertility.

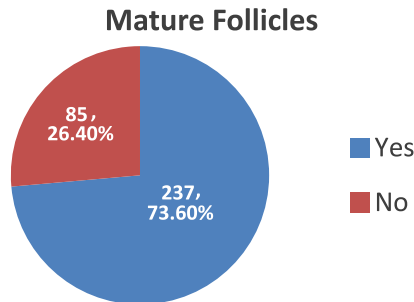
**Table 1:** Baseline Parameters of Patients Having Subfertility due to PCOS (n=322)

Variables	(Mean $\pm$ SD) / N (%)
Age* (Years)	32.82 $\pm$ 4.30
Weight* (Kg)	61.74 $\pm$ 7.35
Height* (m)	1.61 $\pm$ 0.069
BMI* (Kg/m <sup>2</sup> )	23.68 $\pm$ 2.96

Type of Infertility	
Primary	161(50.0)
Secondary	161(50.0)

PCOS = polycystic ovarian syndrome; n = number of study participants; % = percentage of study participants; kg = kilogram; m = meter; BMI= Body mass index; kg/m<sup>2</sup> = kilogram per meter square; \* = mean ± standard deviation was used to explain the data.

Figure 1 illustrated the frequency of mature follicles in patients with PCOS treated with letrozole for subfertility. Among these patients, 237 (73.60%) had mature follicles on ultrasonography after receiving letrozole treatment.



**Figure 1:** Frequency of Mature Follicles in Women with PCOS Treated with Letrozole for Subfertility

Table 2 showed the comparison of mature follicle rate following administration of letrozole with respect to age, body mass index, and type of infertility. Results demonstrated that patients who belonged to 20-30 years age group responded better to letrozole in terms of follicular maturation (p = 0.004). Similarly, patients who were underweight had a significantly higher number of mature follicles following letrozole treatment (p=0.028), as compared to over-weight individuals. Letrozole showed more beneficial impacts in patients having primary infertility (p<0.000).

**Table 2:** Comparison of Mature Follicle Rate Following Administration of Letrozole With Respect to Age, Body Mass Index and Type of Infertility (n = 322)

Variables	Description	Mature Follicle N (%)			p-Value*
		Yes	No	Total	
Age Groups (Years)	20-30	85 (84.16)	16 (15.84)	101 (100.0)	0.004
	31-40	152 (68.78)	69 (31.22)	221 (100.0)	
BMI (Kg/m <sup>2</sup> )	Underweight	4 (100.0)	0 (0.0)	4 (100.0)	0.028
	Normal Weight	148 (69.16)	66 (30.84)	214 (100.0)	
	Over Weight	85 (81.73)	19 (18.27)	104 (100.0)	
Type of Infertility	Primary	133 (82.61)	28 (17.39)	161 (100.0)	0.000
	Secondary	104 (64.60)	57 (35.40)	161 (100.0)	

n = Number of study participants; BMI= Body mass index; kg/m<sup>2</sup> = kilogram per meter square; \* = Chi-square test was utilized to calculate p-value and p≤0.05 was taken significant.

## DISCUSSION

PCOS was the most frequently encountered female endocrine dysfunction responsible for subfertility among

women of reproductive age [22]. Safe and effective induction of ovulation was crucial for women with infertility [18]. So, this study was executed to assess the frequency of mature follicle rate as a result of Letrozole treatment in subfertility due to PCOS. In this interventional study, 322 women with subfertility were included. All patients received Letrozole treatment for follicular maturation. In the present study, mature follicular development was reported in 237 (73.60%) cases in response to Letrozole treatment. In a study by Bansal S et al., mature follicular development was observed in 68.47% patients who received Letrozole treatment [18]. In another study conducted by Hegde R et al., it was reported that mono-follicular development was higher as a result of Letrozole therapy (86.9%). Ovulation rate was also greatly enhanced following Letrozole treatment (92.0%) [23]. Likewise, Javeria M et al., reported that the successful ovulation was achieved in 81% in patients taking Letrozole [24]. A clinical trial carried out by Gupta E et al., revealed that the number of follicles ≥18 mm for the Letrozole group was 1.11 ± 0.43 and 2.53 ± 1.10 for the Clomiphene Citrate group (P<0.001). Letrozole group also had a higher endometrial thickness than the group taking Clomiphene Citrate (P<0.001). Higher ovulation rate was also observed in the letrozole group (P = 0.047), compared to the findings of the present study [25]. Various other studies documented the similar results. In an Indian study, it was found out that ovulation rate was 73% in patients who received a combination of letrozole in comparison to 38% in those who received Letrozole alone (p = 0.003) [6]. Similarly, a Bangladeshi study also reported that mono-follicular development was higher in Letrozole group (p = 0.004) [12]. Another study conducted by Zeba D et al., showed that 65% of patients had ovulation following Letrozole administration [5]. However, an RCT reported that patients who received the combination of letrozole and Clomiphene citrate had a higher ovulation rate (77%) than those who received letrozole alone (43%) this study has several limitations [9]. First, the interventional nature of the study restricts the ability to determine the long-term effects and causality of Letrozole treatment. Secondly, no control group was included in the study, limiting the ability to compare the effects of Letrozole against a baseline or alternative treatments.

## CONCLUSIONS

Letrozole seems to improve the rate of follicle maturation in women with subfertility due to PCOS, thereby increasing the likelihood of pregnancy. Based on these findings, letrozole can be regarded as a suitable alternative to first-line therapies such as clomiphene citrate, providing favorable outcomes and minimal side effects, specifically in patients with clomiphene citrate resistance.

## Authors Contribution

Conceptualization: MJ

Methodology: MJ, SH

Formal analysis: AH

Writing, review and editing: LN, UT, QUAH, SH, AH

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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