

# Comparing Effectiveness of Letrozole Versus Clomiphene Citrate to Evaluate the Ovulation Induction in patients with Polycystic Ovarian Syndrome

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## ABSTRACT

**Background:** Anovulation is the commonest cause of female infertility and polycystic ovarian syndrome (PCOS) is the most frequently seen cause of anovulation among infertile females. Letrozole and Clomiphene Citrate are two common drugs for PCOS. But controversial data was noticed regarding their effectiveness.

**Aim:** To compare effectiveness of Letrozole versus Clomiphene Citrate to evaluate the ovulation induction in patients with polycystic ovarian syndrome

**Methods:** After fulfilling the selection criteria, total 360 females were enrolled according to calculated sample size and were randomly divided into two equal groups. One is treated with letrozole and other is clomiphene citrate. Successful ovulation was noted on follow up. Data was collected in proforma and later on analyzed in SPSS version 23.

**Results:** The mean age of patients in letrozole group was  $26.61 \pm 4.81$  years and in clomiphene citrate was  $27.89 \pm 4.24$  years. Successful ovulation induction was noted in 172 with letrozole and 150 with clomiphene citrate i.e.  $p$ -value=0.001.

**Conclusion:** Letrozole has significantly better efficacy for successful ovulation than Clomiphene Citrate for PCOS.

**Keywords:** Ovulation, Clomiphene citrate, Letrozole, polycystic ovarian syndrome

## INTRODUCTION

Infertility affects 10-15% of the married couples and is a cause of great concern for these couples. Etiologies of infertility can, broadly, be divided into male and female factors<sup>1</sup>. Anovulation is the commonest cause of female infertility and polycystic ovarian syndrome (PCOS) is the most frequently seen cause of anovulation among infertile females<sup>2</sup>. A clinical diagnosis of PCOS can easily be made using Rotterdam Criteria<sup>3</sup>. Infertile females suffering from PCOS often need ovulation induction to achieve conception and there are some options available with variable results. The frequency of PCOS is determined by the diagnostic criteria used. According to the World Health Organization, it affects 116 million women worldwide as of 2010 (about 3.4% females)<sup>4</sup>. According to a community-based prevalence survey using the Rotterdam criterion, approximately 18% of women have PCOS, with 70% of them previously undiagnosed<sup>4,5</sup>.

Since its introduction in 1956, Clomiphene Citrate, a non-steroidal selective estrogen receptor modulator, has been the first line drug for ovulation induction in females with PCOS<sup>2</sup>. Clomiphene Citrate has a high ovulation induction rate (60-85%) but comparatively low pregnancy rate (10-20%), with a higher miscarriage rate (20-25%)<sup>6</sup>. Tamoxifen is another anti-estrogen used for ovulation induction, with no evidence of success over Clomiphene Citrate, in terms of ovulation or pregnancy rates<sup>2</sup>.

Letrozole, an aromatase inhibitor and originally used for chemotherapy in breast cancer, was proposed for ovulation induction, in the year 2000, by Robert Casper and Mohamed F.M. Mitwally<sup>7</sup>. Letrozole inhibits the conversion of androgens to estradiol thus increasing FSH level and also increases FSH receptors in ovarian tissue<sup>8</sup>. It has a short half-life (45 hrs) and it does not cause down regulation of estrogen receptors<sup>9</sup>.

The data available from studies conducted in Pakistan and neighbouring countries, comparing the efficacy of Clomiphene Citrate and Letrozole, are inconclusive. Irum Mobusher from Pakistan and Sujata Kar from India showed almost similar and statistically insignificant results for ovulation rate, endometrial thickness but statistically significant pregnancy rate ( $p=0.0125$ )<sup>6,10</sup>. Fauzia Haq Nawaz demonstrated no statistical difference between the two drugs in terms of endometrial thickness and pregnancy rate ( $p=0.67$  &  $p=0.9$  respectively)<sup>11</sup>. However, Roy *et al.* in their study Letrozole to have statistically better results in terms of endometrial thickness and pregnancy rates ( $p=0.014$  &  $p=0.041$  respectively) when compared to Clomiphene Citrate<sup>12</sup>.

Similarly, Azra Azmoodeh and associates demonstrated higher ovulation and pregnancy rates when treated with Letrozole<sup>8</sup>. This study is being conducted to find out if Letrozole is actually superior to Clomiphene Citrate, to propose and help establish local guideline for ovulation induction, in infertile females suffering from PCOS.

The objective of the study was to compare effectiveness of Letrozole and Clomiphene Citrate (CC), for ovulation induction in patients with PCOS

## PATIENTS AND METHODS

This randomized controlled trial was conducted in Infertility clinic, Rashid Latif Medical College Lahore for a period of 6 months from 1-3-2017 to 1-9-2017 after permission from IRB. Sampling technique used was non probability consecutive sampling.

**Sample size:** Taking the successful ovulation induction rate of 60.78% to Clomiphene Citrate (P1) and 73.08% to Letrozole (P2)<sup>6</sup>, and 05% level of significance and 80% power of test, a sample size of 180 patients per group has been calculated.

**Inclusion Criteria:** All infertile females presenting to infertility clinic with c/o failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. All infertile female patients with established diagnosis of PCOS (Rotterdam Criteria) as the cause of infertility were included with two of the following three criteria:

- Oligo/anovulation i.e. less than 6-9 cycles per year.
- Hyperandrogenism: clinical (hirsutism (Ferriman-Gallway score >8) or less commonly male pattern alopecia) or biochemical (raised FAI or free testosterone)
- Polycystic ovaries on ultrasound i.e.  $\geq 12$  Antral follicles in one ovary or ovarian volume  $\geq 10\text{cm}^3$ .

**Exclusion Criteria:** Females from couples with male factor infertility, endometriosis, tubal, uterine and/or cervical pathology as the cause of infertility, diagnosed endocrine disorder, taken any treatment for infertility previously.

**Data collection:** 250 infertile females with established diagnosis of anovulation as the cause of infertility, who fulfilled the inclusion and exclusion criteria, was enrolled to the study. All of the study participants were provided details about the conduct of the study, including the details of the drugs under study and randomization process. They were also informed about their right to withdraw from study, at any time, without having any fear of refusal of treatment. A written informed consent was obtained from each study participant, mentioning their willingness to participate in the study and for use of their data for study and publication. Demographic information

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i.e. age, education, and duration of infertility was collected. Each participant inquired about the duration and regularity of her menstrual cycle. The study group was assigned to the participant by using random number table. Patients in Group 1 received Letrozole 2.5mg per day (oral), from day 2 to day 6 of their menstrual cycle. Patients in 2 group received Clomiphene Citrate 50mg per day (oral) from day 2 to day 6 of the cycle. All the patients, in both groups, were evaluated for ovulation, number and size of ovarian follicle and endometrial thickness through TVS done by a single consultant sinologist (to avoid discrepancy of measurements due to individual skills). Patients in both groups were treated and assessed for outcome variables i.e. follicular development and endometrial thickness, for one menstrual cycle only. Effectiveness was measured in terms successful ovulation induction i.e. follicular development and endometrial thickness. During one cycle only. Successful ovulation induction, assessed by at least one ovarian follicle with the size  $\geq 18\text{mm}$  is found, on TVS, from day 12 to day 18 of the cycle and Endometrial thickness of 6mm or more with trilaminar pattern. All the participants were provided further treatment as per standard operating procedures of the institute. All this information collected on Performa.

**Data analysis:** All the data collected was analyzed using SPSS version 23. Descriptive Statistics was calculated. Quantitative data like pattern of duration of infertility. Qualitative data like pattern of menstrual cycle in term of (2-5, 6-10>11 years) and effectiveness successful ovulation induction will be presented as frequencies and percentages. Age and endometrial thickness was presented as mean and standard deviation.

**RESULTS**

The mean age of the patients in letrozole group was  $26.61 \pm 4.81$  years and in clomiphene citrate was  $27.89 \pm 4.24$  years. The mean duration of infertility in letrozole group was  $4.11 \pm 3.50$  years and in clomiphene citrate was  $4.70 \pm 3.404$  years. The regular pattern of menstrual cycle was found in 179 cases in which 96 were from letrozole group and 83 were from clomiphene citrate group, similarly the irregular pattern was found in 181 cases in which 84 were from letrozole group and 7 were from clomiphene citrate group. In our study the monofollicles were noted in 176 cases in which 95 were from letrozole group and 81 were from clomiphene citrate group, similarly the multi-follicular patients were 184 in which 85 were from letrozole group and 99 were from clomiphene citrate group (Table 1).

The mean ET at day 12 in letrozole group was  $4.72 \pm 0.95$  and in clomiphene citrate group was  $4.42 \pm 0.99$ . The mean ET at day 14 in letrozole group was  $6.10 \pm 1.210$  and in clomiphene citrate group was  $5.67 \pm 1.17$ . The mean ET at day 16 in letrozole group

In this study, successful ovulation induction was noted in 322(89.44%) patients and unsuccessful ovulation induction was found in 38(10.56%) patients (Fig 1).

In our study the successful ovulation induction was found in 322 cases in which 172 were randomized to letrozole group and 150 were randomized to clomiphene citrate group, similarly the unsuccessful ovulation induction was noted in 38 cases in which 8 females had letrozole and 30 females had clomiphene citrate. Statistically, the difference was significant in both groups for ovulation induction i.e. p-value=0.001 (Table 3). In patients with age  $\leq 30$  years, the successful ovulation induction was noted in 226 patients in which 126 were from letrozole group and 100 were from clomiphene citrate group, similarly in patients with age  $> 30$  years the successful ovulation induction was noted in 96 cases in which 46 were from letrozole group and 50 were from clomiphene group. Statistically, the difference was significant i.e. p-value<0.05. In patients with duration of infertility  $\leq 10$  years, the successful ovulation induction was noted in 297 patients in which 158 were from letrozole group and 139 were from clomiphene citrate group,

was  $7.29 \pm 1.310$  and in clomiphene citrate group was  $6.62 \pm 1.469$ . In this study the mean ET at day 18 in letrozole group was  $8.09 \pm 1.405$  and in clomiphene citrate group was  $7.28 \pm 1.427$ . Statistically, the difference was significant in both groups i.e. p-value<0.05 on each visit (Table 2).

Table 1: Demographics of females

	Study groups	
	Letrozole	Clomiphene citrate
n	180	180
Age (years)	$26.61 \pm 4.81$	$27.89 \pm 4.24$
Duration of infertility	$4.11 \pm 3.50$	$4.70 \pm 3.40$
<b>Pattern of menstrual cycle</b>		
Regular	96	83
Irregular	84	97
<b>No. of follicles</b>		
Monofollicular	95	81
Multi-follicular	85	99

Table 2: Comparison of endometrial thickness at day 12 with study groups

Endometrial thickness(cm)	Study Groups		P value
	Letrozole	Clomiphene citrate	
n	180	180	
Day 12	$4.72 \pm 0.95$	$4.42 \pm 0.99$	0.004
Day 14	$6.10 \pm 1.21$	$5.67 \pm 1.17$	0.01
Day 16	$7.29 \pm 1.31$	$6.62 \pm 1.47$	0.001
Day 18	$8.09 \pm 1.41$	$7.28 \pm 1.43$	0.001

Fig 1: Frequency distribution of ovulation induction

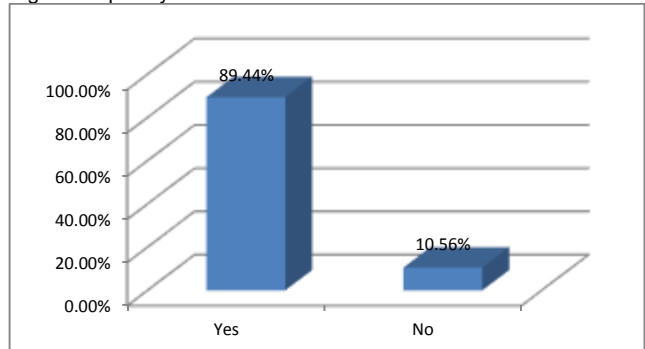


Table 3: Comparison of ovulation induction in both groups

Ovulation induction	Study Groups		Total
	Letrozole	Clomiphene citrate	
Yes	172	150	322
No	8	30	38
Total	180	180	360

Similarly in patients with duration of infertility  $> 10$  years the successful ovulation induction was noted in 25 cases in which 14 were from letrozole group and 11 were from clomiphene group. Statistically, the difference was significant i.e. p-value=0.001. In patients with regular pattern of menstrual cycle, the successful ovulation induction was noted in 157 patients in which 90 were from letrozole group and 67 were from clomiphene citrate group, similarly in patients with irregular pattern of menstrual cycle the successful ovulation induction was noted in 165 cases in which 82 were from letrozole group and 83 were from clomiphene group. Statistically, the difference was significant i.e. p-value<0.05. In patients with mon-follicular, the successful ovulation induction was noted in 163 patients in which 92 were from letrozole group and 71 were from clomiphene citrate group, similarly in patients with multiple-follicular, the successful ovulation induction was noted in 159 cases in which 80 were from letrozole group and 79 were from clomiphene group. Statistically, the difference was significant in both groups i.e. p-value=<0.05. (Table 4).

Table 4: Comparison of ovulation induction with study groups stratified for effect modifiers

Age (years)	Ovulation induction	Study Groups		Total	p-value
		Letrozole	Clomiphene citrate		
≤ 30	Yes	126	100	226	0.007
	No	8	20	28	
> 30	Yes	46	50	96	0.005
	No	0	10	10	
<b>Duration of infertility</b>					
≤ 10	Yes	158	139	297	0.001
	No	8	27	35	
> 10	Yes	14	11	25	0.222
	No	0	3	3	
<b>Pattern of menstrual cycle</b>					
Regular	Yes	90	67	157	0.008
	No	6	16	22	
Irregular	Yes	82	83	165	0.007
	No	2	14	16	
<b>No. of follicles</b>					
Mono-follicular	Yes	92	71	163	0.039
	No	3	10	13	
Multiple-follicular	Yes	80	79	159	0.005
	No	5	20	25	

## DISCUSSION

One of the most common causes of reproductive failure in infertile couples is ovarian dysfunction. Infertile people have a 30% to 40% chance of developing this condition. PCOS is a common condition that is linked to ovulation deficiency and affects 7% of women of childbearing age. Clomiphene citrate is the most commonly prescribed oral ovulation inducer. Letrozole is a nonsteroidal aromatase inhibitor that was initially used to treat postmenopausal breast cancer and is currently the only permitted indication<sup>13,14</sup>.

In our study the successful ovulation induction was noted in 322 cases in which 172 were from letrozole group and 150 were from clomiphene citrate group. Statistically, significant difference has been observed in both groups for ovulation induction (p-value=0.001). In our study significantly higher ET value was noted in letrozole group than to Clomiphene Citrate group. A study by Mobasher et al.,<sup>15</sup> documented a higher rate of mono-follicular development and conception when letrozole was given for ovulation induction in females with complaint of infertility due to PCOS, which was statistically significant (p<0.05). Letrozole was reported to be significantly better for ovulation induction in females who were resistant to the Clomiphene Citrate. Hyperinsulinemia, which is significantly related to the PCOS, is considered as the major contributory risk factor for resistance against Clomiphene Citrate<sup>16</sup>.

Roy *et al*, in their study Letrozole to have statistically better results in terms of endometrial thickness and pregnancy rates ( $p=0.014$  &  $p=0.041$  respectively) when compared to Clomiphene Citrate<sup>12</sup>. Azra Azmoodeh and associates demonstrated higher ovulation and pregnancy rates when treated with Letrozole<sup>9</sup>. Badawy *et al.*, recorded statistically slightly higher endometrial thickness in the Clomiphene Citrate group (9.20.7) vs. letrozole (8.10.2,  $P=0.021$ ) in their sample of 438 patients with 1063 cycles, one of the largest trials comparing Clomiphene Citrate and letrozole.<sup>17</sup> Few trials have shown a substantial variation in endometrium effects between the two classes<sup>18,19</sup>.

Banerjee *et al.*, compared letrozole (2.5 mg) to clomiphene in 147 Indian women with PCOS in a recent report (100 mg). The mean endometrial growth in the letrozole community was 8.7211.41 mm, whereas it was 8.781.16 mm in the Clomiphene Citrate group ( $P=0.004$ )<sup>18</sup>. Letrozole was linked to increased endometrial thickness, according to Mitwally and Casper<sup>20</sup>. According to a study conducted by Xi *et al.*, Letrozole combined with HMG is an important protocol for minimizing the chances of hyperstimulation for ovarian induction in Clomiphene Citrate-resistant women with PCOS. In patients that are especially vulnerable to gonadotropin, this formulation could be more suitable<sup>21</sup>.

The mean endometrial growth was 8.72 1.41mm in the

letrozole group and 8.78 1.16mm in the clomiphene group ( $P=0.004$ ), according to an analysis by Banerjee *et al*. Letrozole has a positive effect on the endometrium, theoretically increasing pregnancy rates in women with PCOS following successful ovulation induction.<sup>18</sup> In a meta-analysis by He & Jiang, the therapeutic effectiveness of letrozole for ovulation induction in PCOS women was linked to clomiphene. This is one of the most comprehensive meta-analyses of the topic ever written<sup>22</sup>.

Six randomized trials with a total of 841 patients were examined. There were no major variations between the two classes in terms of fertility rates, abortion rates, or multiple birth rates. Irum Mobasher from Pakistan and Sujata Kar from India had nearly identical and statistically negligible ovulation and endometrial thickness outcomes, but a statistically important pregnancy rate (p-value = 0.0125)<sup>6,10</sup>. In terms of endometrial thickness and conception incidence, Fauzia Haq Nawaz found no statistical discrepancy between the two treatments (p-value >0.05)<sup>11</sup>.

Infertility is one of the common problems that face women with PCOS and the FSH and Clomiphene Citrate are the principal treatments used for anovulating women. Gonadotropins are used to induce ovulation in women with PCOS who do not respond to Clomiphene Citrate. Also lowering insulin levels by using insulin-sensitising drugs such as biguanides and thiazolidinediones may restore fertility. The laparoscopic ovarian surgery "ovarian drilling" is used to induce ovulation in Clomiphene Citrate resistance women with anovulatory PCOS. Other option for achieving pregnancy in women with PCOS is to use in Vitro Fertilization<sup>23</sup>

## CONCLUSION

Our study proved that Letrozole group showed significantly better efficacy in terms of ET and successful ovulation induction than to Clomiphene Citrate group in patients with PCOS.

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