



## COMPARISON OF EFFICACY BETWEEN LETROZOLE AND CLOMIPHENE CITRATE IN FEMALES PRESENTED WITH INFERTILITY DUE TO POLYCYSTIC OVARIES.

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### Abstract:

**Background:** Polycystic ovarian syndrome (PCOS) is a genetically heterogeneous syndrome in which females often have to confront with the issue of infertility. Medical management of PCOS is aimed at the treatment of anovulation and menstrual irregularity. Letrozole and clomiphene citrate are two successful drugs for management of PCOS but contradiction is present in literature that which drug is more effective. So we conducted this study to find more successful drug to be implemented in future in local population.

**Objective:** To compare the efficacy of oral Letrozole versus Clomiphene Citrate in females diagnosed with infertility due to polycystic ovaries

**Subjects & Methods:** This randomized control trial was conducted at department of Gynaecology & Obstetrics, Fatima Memorial Hospital, Lahore for 6 months (May to November 2020). The non-probability, consecutive Sampling was used. Informed consent and demographic data was noted. Then females were randomly divided in two group by using lottery method. Females in Letrozole group were prescribed 2.5-7.5 mg daily from Day 2-Day 6 of menstruation and females in clomiphene citrate group was prescribed 50-150 mg daily from Day 2-Day 6 of menses. Females were advised to visit after every cycle till 3months. On every visit transvaginal ultrasonography was done to assess presence of follicles and number and size of follicles and endometrial thickness. All the data was entered on SPSS version 20.

**Results:** The mean age of the patients was 26.13±5.07 years in group A and 27.17±5.95 years in group B. After 3<sup>rd</sup> month, the mean endometrial thickness in group A was 8.45±0.58 mm and in group B was 7.45±0.58 mm, the mean follicle was 23.75±4.253 in group A while 20.38±6.154 in group B. The ovulation occurred in 48 cases in group A and in 29 cases in group B. The efficacy was achieved in 36 cases in group A and 16 cases in group B and the difference in both groups was statistically significant i.e. p-value=0.000.

**Conclusion:** Thus the Letrozole has significantly higher efficacy as compared to Clomiphene citrate. So from the results of our study we recommend letrozole as first line treatment for the management of PCOS.

**Keywords:** Polycystic ovarian syndrome, PCOS, Letrozole, Clomiphene Citrate, Efficacy, Infertility

### Introduction:

Dysfunction of ovulatory system is the most common basis of failure of reproductive system in females with complaint of infertility. The prevalence of infertility due to polycystic ovaries is around 30-40%. Polycystic ovaries are common disease in females of reproductive age group, which is narrowly associated with ovulation dysfunction and effects around 7% females of reproductive age.<sup>1</sup> The main cause of this diverse ailment is still unclear and its phenotype manifestation fluctuates.<sup>2</sup> Induction of ovulation is the way to manage infertility in females with PCOS, which can be done via medication or surgery.<sup>1</sup> Clomiphene citrate is the long-lasting, standard medicine to induce ovulation. It is

still thought as the first line medication for treatment of polycystic ovaries in females.<sup>2,3</sup>

Estrogens are produced by conversion of the androgens via the activity of aromatase enzymes. Estrogens then join the estrogens receptors, which leads the cells to split. Letrozole averts the aromatase from generating the estrogens by competitive, adjustable binding to heme of its cytochrome-P450 unit. The phenomena is precise and letrozole does not lessen the production of mineralocorticoids or corticosteroids.<sup>4</sup> Letrozole has no harmful effects on the endometrium and on cervical mucus. Letrozole has proved its effect on good ovulation and showed more ovulation in females with Clomiphene citrate resistance for polycystic ovaries.<sup>5</sup>

Nahid and Sirous conducted a study and reported that the ovulation rate was 88%; for both drugs.<sup>1</sup> Letrozole has been found as effective as old traditional drug i.e. clomiphene citrate for induction of ovulation and attaining pregnancy in females diagnosed with polycystic ovarian syndrome.<sup>3</sup> But controversies also exist. Kamath and George found that the difference between Letrozole and Clomiphene citrate for induction of ovulation was 82.4% versus 63.6%, respectively (p-value = 0.01).<sup>8</sup> But authors concluded that letrozole has the complete role in females with anovulation who did not respond to the clomiphene citrate therapy. Although its role as the substitute to the first line therapy i.e. clomiphene citrate is still under debate. However, it is apparent that the overall benefits of letrozole exceed the clomiphene citrate, existing data still not approve this assessment. So large randomized, well-designed trials are required to be done to confirm this evidence.<sup>8</sup>

Rationale of this study is to compare the efficacy of Letrozole and Clomiphene Citrate in females presenting with infertility due to polycystic ovaries. Literature has reported that Letrozole is better regimen for resolution of PCO and ovulation induction but due to controversy and disagreement in results, gynaecologists rely on conventional method i.e. clomiphene citrate. Through this study we want to confirm whether we can rely on letrozole for ovulation induction or not. So that in future we can implement the results of this study and can replace Clomiphene citrate with letrozole as it seems to be more effective and beneficial for infertile females. This can help to achieve more patient satisfaction and can improve our practice and update guidelines to manage PCO.

#### **Objective:**

To compare the efficacy of oral Letrozole versus Clomiphene Citrate in females diagnosed with infertility due to polycystic ovaries

#### **Materials & Methods:**

**Study design:** Randomized Controlled Trial

**Place of study:** Department of Gynecology & Obstetrics, Fatima Memorial Hospital, Lahore.

**Study period:** Six months i.e. May to November 2020

**Sample size:** Total sample of 120 cases (60 cases in each group) was estimated by using 80% power of test, 5% significance level and percentage of efficacy i.e. 78.7%<sup>9</sup> of Letrozole and 53.3%<sup>9</sup> of Clomiphene citrate in females with infertility due to polycystic ovaries.

**Sample technique:** Nonprobability, consecutive Sampling

**Patient selection:** Married females of age 18 to 35 years with diagnosis of PCOS were included. Polycystic ovaries was labeled as presence of  $\geq 12$  follicles of 2-9mm and ovaries volume  $>10\text{cm}^3$  on ultrasound and LH/FSH ration will be  $> 1$  IU/L (Normal value is 1 IU/L). Females with diabetes (BSR $>186\text{mg/dl}$ ), hypertension (BP $>140/90$

through medical record and history), renal dysfunction (serum creatinine $>1.2\text{mg/dl}$ ), liver dysfunction (AST $>40\text{IU}$ , ALT $>40\text{IU}$ ), females allergic to letrozole or clomiphene citrate, already have taken medication of letrozole or clomiphene citrate were excluded.

**Data collection procedure:** Consent form was taken and demographics were noted. All the recruited females were divided randomly into two equal group by using the lottery method. Females in Letrozole group were prescribed 2.5-7.5 mg daily from Day 2-Day 6 of menstruation and females in clomiphene citrate group was prescribed 50-150 mg daily from Day 2-Day 6 of menses. Females were advised to visit after every cycle till 3months. On every visit transvaginal ultrasonography was done to assess presence of follicles and number and size of follicles and endometrial thickness. Efficacy was labeled, when endometrial thickness of  $>8\text{mm}$  and size of follicle 18-22mm after 3 months cycle of treatment). All this information was recorded on proforma (attached).

**Data Analysis:** SPSS v. 20 was used to enter and analyze the data. Chi-square was applied to compare both groups for efficacy keeping p-value  $\leq 0.05$  as significant.

#### **Results:**

The mean age of the patients was  $26.13 \pm 5.07$  years in group A and  $27.17 \pm 5.95$  years in group B. In our study the mean marriage duration of group A patients was  $2.12 \pm 0.99$  years and the mean marriage duration value in group B patients was  $2.07 \pm 1.05$  years. Table 1

In this study the mean value of endometrial thickness after the 1<sup>st</sup> month of group A patients was  $5.95 \pm 0.58$  and its mean value in group B patients was  $5.05 \pm 0.58$ . The study results showed that the mean value of endometrial thickness after the 2<sup>nd</sup> month of group A patients was  $6.95 \pm 0.58$  and its mean value in group B patients was  $5.950 \pm 0.58$ . The mean value of endometrial thickness after the 3<sup>rd</sup> month of group A patients was  $8.45 \pm 0.58$  and its mean value in group B patients was  $7.45 \pm 0.58$ . The mean value of follicle after the 1<sup>st</sup> month of group A patients was  $22.10 \pm 4.513$  and its mean value in group B patients was  $19.30 \pm 5.864$ . The mean value of follicle after the 2<sup>nd</sup> month of group A patients was  $23.43 \pm 4.496$  and its mean value in group B patients was  $19.45 \pm 6.124$ . The mean value of follicle after the 3<sup>rd</sup> month of group A patients was  $23.75 \pm 4.253$  and its mean value in group B patients was  $20.38 \pm 6.154$ . The study results showed that the ovulation after 1<sup>st</sup> month was observed in 14 cases in group A and in 6 cases in group B. The ovulation after 2<sup>nd</sup> month was observed in 29 cases in group A and in 15 cases in group B. The ovulation after 3<sup>rd</sup> month was observed in 48 cases in group A and in 29 cases in group B. The efficacy was achieved in 36 cases in group A and 16 cases in group B and the difference in both groups was statistically significant i.e. p-value=0.000. Table 2

**Table 1: Comparison of demographics in both groups**

	Study Groups	
	Letrozole	Clomiphene Citrate
<b>n</b>	<b>60</b>	<b>60</b>
<b>Age (years)</b>	26.13 ± 5.07	27.17 ± 5.95
<b>Marriage duration (years)</b>	2.12 ± 0.99	2.07 ± 1.05

**Table 2: Comparison of uterine features during follow-up in both groups**

Endometrial thickness	Study Groups		p-value
	Letrozole	Clomiphene Citrate	
<b>n</b>	60	60	
<b>1<sup>st</sup> month</b>	5.95 ± 0.58	5.05 ± 0.58	0.000
<b>2<sup>nd</sup> month</b>	6.95 ± 0.58	5.95 ± 0.58	0.000
<b>3<sup>rd</sup> month</b>	8.45 ± 0.58	7.45 ± 0.58	0.000
<b>Follicle size</b>			
<b>1<sup>st</sup> month</b>	22.10 ± 4.51	19.30 ± 5.86	0.004
<b>2<sup>nd</sup> month</b>	23.43 ± 4.50	19.45 ± 6.12	0.000
<b>3<sup>rd</sup> month</b>	23.75 ± 4.25	20.38 ± 6.15	0.001
<b>Ovulation occurred at</b>			
<b>1<sup>st</sup> month</b>	14	6	0.050
<b>2<sup>nd</sup> month</b>	29	15	0.008
<b>3<sup>rd</sup> month</b>	48	29	0.000
<b>Efficacy achieved</b>	36	16	0.000

**Discussion:**

Polycystic ovaries are the most common endocrinopathic disease in females which occurs due to infertility due to anovulation in females of reproductive age groups. Clomiphene citrate is used for induction of ovulation in females with polycystic ovaries. It was approved for use in 1960s. Clomiphene citrate is still used as the first line medicine for induction of ovulation in females with polycystic ovaries. Letrozole is the type of aromatase inhibitor. Researchers have explored the letrozole as the good substitute of clomiphene citrate, but the existing data regarding its success in induction of ovulation in comparison to clomiphene citrate is still controversial.<sup>10,11</sup>

There are several clinical exhibitions of the polycystic ovaries syndrome, and the infertility because of chronic anovulation is the most common manifestation. Clomiphene citrate has been used since 1960's and still in use. It is still considered as the long standing, and standard medicine for induction of ovulation in infertile females. It is used as the first-line preference in females with polycystic ovaries. Although, the clomiphene citrate has few definite distinct disadvantages. Treatment of polycystic ovaries by using Clomiphene citrate is related to the inconsistency in the frequency of ovulation (60-85%) and pregnancy (10-20%). The rate of miscarriages is also higher with clomiphene citrate as compared to the general population, and 20-25% of females with polycystic ovaries who has resistance to the clomiphene citrate. Anti-estrogenic effects of Clomiphene citrate causes the long-term weakening of the estrogen receptors, harmfully affecting the endometrial growth and

progress in addition to the quality and quantity of cervical mucus.<sup>17</sup>

In our study, the mean age of patients was 26.13±5.07 years in group A and 27.17±5.95 years in group B. In a study by Razzaq, the mean age of females was 26.56 ± 4.17 years with majority of patients (64.15%) aged between 21-30 years. These findings were also similar to the studies conducted by Fouda et al.,<sup>12</sup> and Sherif et al.,<sup>13</sup> who showed the mean age of females with polycystic ovaries as 26 and 27 years, respectively. Hussain et al.,<sup>9</sup> conducted a trial and observed the mean age of females as 29 years, which was higher than we observed in our study.

According to the results of our trial, the efficacy (ovulation) occurred in 36 females with letrozole while in 16 females with clomiphene citrate. Statistically, the letrozole showed significantly better efficacy than Clomiphene citrate.

In one meta-analysis conducted by He & Jiang,<sup>14</sup> and compared the clinical efficacy and safety of letrozole and clomiphene citrate for ovulation induction in females with polycystic ovaries. A study, conducted by Razzaq et al., it was presented that the mean duration of marriage was 4.06±1.95 years with letrozole and 4.26±2.12 years with clomiphene citrate. The efficacy of clomiphene citrate was achieved in 10.38% cases while in 21.70% cases with letrozole (p-value = 0.02) which is consistent with findings of our study.<sup>15</sup> Atay et al.,<sup>16</sup> in a randomized trial, compared the letrozole and clomiphene citrate in the treatment of infertility due to anovulation and observed the letrozole as more effective than clomiphene citrate. Researchers observed that the frequency of ovulation was achieved in 82.4% versus 63.6% (p-value = 0.01) while the

frequency of confirm pregnancy was 21.6% versus 9.1% (p-value = 0.03). Thus letrozole was significantly more effective as compared to clomiphene citrate.

Roy *et al.*,<sup>7</sup> conducted another trial and compared the letrozole with clomiphene citrate ovulation induction and conceiving the pregnancy in females of reproductive age group. They observed that the frequency of efficacy was significantly higher with letrozole (43.8%) than clomiphene citrate (26.4%, p-value < 0.05). While the trial conducted by Kar *et al.*,<sup>17</sup> showed that the letrozole was more effective in achieving excellent pregnancy as compared to the clomiphene citrate. Letrozole must be deliberated as equal as clomiphene citrate as the first line medicine for induction of ovulation in infertile females with polycystic ovaries, but the ovulation and endometrial thickness were insignificantly differ in both groups (p-value = 0.398).

In one more randomized trial, conducted by Hussain *et al.*,<sup>9</sup> the frequency of pregnancy was found significantly higher with Letrozole as compared to Clomiphene citrate i.e. 25.3% versus 16.0%, respectively; but, this was statistically insignificantly. Badawy *et al.*,<sup>6</sup> conducted one of the largest trial that compared the letrozole and Clomiphene citrate. They included total 438 females with 1,063 cycles, and found significantly high endometrial thickness with Clomiphene citrate ( $9.2 \pm 0.7$ ) as compared to the letrozole ( $8.1 \pm 0.2$ , P-value = 0.021). Another similar trial, conducted by Begum *et al.*,<sup>18</sup> on 64 adult females with polycystic ovaries who had resistance against 100 mg clomiphene citrate in Bangladesh. Researchers observed that the females who were resistant to clomiphene citrate showed high pregnancy rate (40.63%) with letrozole than 150 mg Clomiphene citrate i.e. 15%. But conflicting data has also been observed in literature. Kamath & George conducted one randomized trial and observed the difference of Letrozole and Clomiphene citrate for induction of ovulation was significant and rate of ovulation was 82.4% versus 63.6%, respectively.<sup>8</sup>

### Conclusion:

It has been found though findings of our study that Letrozole had significantly higher efficacy as compared to clomiphene. So from the results of our study we recommend letrozole as first line treatment for the management of PCOS.

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