

# Comparison Between Clomiphene Citrate and Letrozole in Patients with Polycystic Ovarian Syndrome in Terms of Monofollicular Development

Comparison between Clomiphene and Letrozole in Polycystic Ovarian Syndrome

Maria Tariq<sup>1</sup>, Hira Suleman<sup>1</sup>, Madiha Khadim<sup>2</sup>, Madiha Shaheen<sup>1</sup> and Noreen Tahir<sup>1</sup>

## ABSTRACT

**Objective:** The objective of this study was to compare clomiphene citrate and Letrozole in patients with polycystic ovarian syndrome in terms of monofollicular development.

**Study Design:** Randomized control trial study.

**Place and Duration of Study:** This study was conducted at the Gynae Unit 1 Outpatient department, Holy Family Hospital Rawalpindi from January 2019 to December 2019.

**Materials and Methods:** The patients fulfilling the inclusion /exclusion criteria were divided into two groups by lottery method. Group A was given clomiphene citrate 100 mg as a single dose from day 2 to day 5 of menstrual cycle. Group B was given 5 mg letrozole as a single dose from day 2 to day 5 of menstrual cycle. The patients were followed by transvaginal scan for follicular tracking on day 11 and 13 of cycle. This ultrasound was conducted by PGT 4 or SR. Monofollicular formation was observed on TVS.

**Results:** In group A, PCOS was diagnosed in 30.67% patients by oligomenorhea, 32% by weight gain, hirsutism, 21.33% by increased LH levels and 16% by ultrasound. In group B, PCOS was diagnosed in 33.33% patients by oligomenorhea, 32% by weight gain, hirsutism, 18.67% by increased LH levels and 16% by ultrasound. Monofollicular formation was observed in 57.33% patients in group A and in group B Monofollicular formation was found in 78.67% patients. In group A, there were 49.33% patients in which primary infertility was detected and 50.67% patients in which secondary infertility was found. In group B, there were 54.67% patients in which primary infertility was detected and 45.33% patients in which secondary infertility was found.

By using t-test, there was no significant difference of age in both groups having p-value = 0.49. There was no significant difference found of marriage duration in both groups having p-value = 0.86. Significant difference of parity was found in both groups having p-value = 0.05.

By using chi-square test, there was significant association found between study groups and monofollicular formation. Monofollicular formation was significantly lower in group A having p-value = 0.005. There was no significant association found between age and monofollicular formation having p-value = 0.775. Marriage duration was not significantly associated with monofollicular formation having p-value = 0.085. Parity was not significantly associated with monofollicular formation having p-value = 0.475.

**Conclusion:** Letrozole is better as compared to Clomiphene citrate in terms of monofollicular development in patients with PCOs. Effect modifiers have not significant association with monofollicular formation.

**Key Words:** Polycystic Ovarian Syndrome, Clomiphene Citrate and Letrozole, Monofollicular Formation

**Citation of article:** Tariq M, Suleman H, Khadim M, Shaheen M, Tahir N. Comparison Between Clomiphene Citrate and Letrozole in Patients with Polycystic Ovarian Syndrome in Terms of Monofollicular Development. Med Forum 2020;31(8):68-71.

## INTRODUCTION

<sup>1</sup>. Department of Gynae & Obstet, Shifa College of Medicine, Islamabad.

<sup>2</sup>. Department of Gynae & Obstet, HBS Medical and Dental College, Islamabad.

Correspondence: Dr. Madiha Khadim, Senior Registrar, HBS Medical and Dental College, Islamabad.

Contact No: 0333-5713298

Email: Madiha.rizwan13@gmail.com

Received: April, 2020

Accepted: May, 2020

Printed: August, 2020

Polycystic ovary syndrome (PCOS), is a complex endocrine disorder with multi-system manifestations making it a therapeutic challenge for the treating team. Since its recognition first in 1935, it has been diagnosed very commonly among women all around the world<sup>1</sup>.

Androgen excess, ovulatory dysfunction, and/or polycystic ovaries have been main clinical features of this complex disorder<sup>2</sup>.

Polycystic ovary syndrome (PCOS) has a variable epidemiology depending upon the type of population studies and the criteria used for diagnosis<sup>3</sup>. Even the international societies and health related organizations have different opinions regarding the type of criteria used to diagnose this disorder and parameters included in the criteria<sup>4</sup>. NIH 1990 criteria has been usually used

for clinical diagnosis of this condition. Using this criteria, variable statistics have been generated among various populations around the globe.<sup>5-10</sup>

PCOS may give rise to multiple problems like oligoovulatory infertility, Obesity and/or insulin resistance, diabetes mellitus (type I, II or gestational), history of premature adrenarche, first-degree relatives with PCOS<sup>11-14</sup>. Epilepsy or anti-epileptic drugs have also been linked with this disorder. Valproate has very strong association with this disorder so should most likely be avoided among young females<sup>14</sup>. Our main focus has been the treatment options for this multi-system disorder therefore this study was planned with the rationale to compare clomiphene citrate and Letrozole in patients with polycystic ovarian syndrome in terms of monomolecular development.

## MATERIALS AND METHODS

This Randomized control trial was conducted at Gynae unit 1 Outpatient department, Holy Family Hospital Rawalpindi from January 2019 to December 2019. Sample size was calculated but using the WHO calculator with Power of test =90%, Level of Significance=5%, P1 55.7% and P2 78.32%.

Sample size turned out to be 75 in each group. Non-probability consecutive sampling was used to gather the sample. Patients with PCOs age ranging from 20-35 years were included in the study. Patients with tubal diseases or local cause of infertility (vaginal discharge) or cervical diseases or couples with male factor of infertility were excluded from the study.

The study was started after approval of ethical committee. The patients fulfilling the inclusion/exclusion criteria were divided into two groups by lottery method. Group A was given clomiphene citrate 100 mg as a single dose from day 2 to day 5 of menstrual cycle. Group B was given 5 mg letrozole as a single dose from day 2 to day 5 of menstrual cycle. The patients were followed by transvaginal scan for follicular tracking on day 11 and 13 of cycle. This ultrasound was conducted by PGT 4 Or SR. Monofollicular formation was observed on TVS.

PCOS: The diagnosis of PCOS was made on either of the following criteria.

- a) Oligomenorhea: Menses occurring at interval of six weeks to six months
- b) Weight gain (BMI > 25kg /m<sup>2</sup>), hirsutism (Excessive hair growth in different parts of body like upper limb, chin, breast, abdomen, arms and legs).
- c) Increase Serum LH: >10 IU in mid Follicular phase of menstrual cycle.
- d) Polycystic ovaries on ultrasound.:12 or more follicles with a diameter of 2-9 mm or ovarian volume >10mm observed on abdominal scan or TVS (trans vaginal scan)

Clomiphene citrate: I used 100 mg clomiphene citrate as single dose given from day 2 to day 5 of menstrual cycle.

Letrozole: I used 5 mg letrozole as single dose given from day 2 to day 5 of menstrual cycle.

Monofollicle; Formation of 1 dominant follicle of 20 cm which was observed on day 11th and 13th on TVS. We used SPSS version 20.0 for our data analysis. Quantitative variables like age, parity were measured as mean  $\pm$  SD. Qualitative variables like monofollicular formation were measured as frequency and percentages. Chi-square test was applied to compare monofollicular formation between two groups. P value  $\leq$  0.05 was considered as significant. Effect modifiers like age, parity, primary, secondary infertility were controlled by stratification. Post stratification Chi-square test was applied. P value  $\leq$  0.05 was considered as significant.

## RESULTS

In group A, the mean + standard deviation of age was found as 28.25 + 4.43 years and 28.76 + 4.53 years in group B. The mean + standard deviation of marriage duration was found as 4.15 + 1.87 years in group A and 4.20 + 1.84 years in group B. The mean + standard deviation of parity was found as 0.72 + 0.89 in group A and 1.07 + 1.25 in group B.

In group A, PCOS was diagnosed in 23 (30.67%) patients by oligomenorhea, 24 (32%) by weight gain, hirsutism, 16 (21.33%) by increased LH levels and 12 (16%) by ultrasound. In group B, PCOS was diagnosed in 25 (33.33%) patients by oligomenorhea, 24 (32%) by weight gain, hirsutism, 14 (18.67%) by increased LH levels and 12 (16%) by ultrasound. Monofollicular formation was observed in 43 (57.33%) patients in group A and in group B Monofollicular formation was found in 59 (78.67%) patients. In group A, there were 37 (49.33%) patients in which primary infertility was detected and 38 (50.67%) patients in which secondary infertility was found. In group B, there were 41 (54.67%) patients in which primary infertility was detected and 34 (45.33%) patients in which secondary infertility was found.

By using t-test, there was no significant difference of age in both groups having p-value = 0.49. There was no significant difference found of marriage duration in both groups having p-value = 0.86. Significant difference of parity was found in both groups having p-value = 0.05.

By using chi-square test, there was significant association found between study groups and monofollicular formation. Monofollicular formation was significantly lower in group A having p-value = 0.005. There was not significant association found between age and monofollicular formation having p-value = 0.775. Marriage duration was not significantly associated with monofollicular formation having p-

value = 0.085. Parity was not significantly associated with monofollicular formation having p-value = 0.475.

**Table No.1: Comparison of Age, Marriage Duration and Parity in both groups**

Variables	Group	n	Mean + Std. Deviation	P-value
Age	Group A	75	28.25 + 4.43	0.49
	Group B	75	28.76 + 4.53	
Marriage Duration	Group A	75	4.15 + 1.87	0.86
	Group B	75	4.20 + 1.84	
Parity	Group A	75	0.72 + 0.89	0.05
	Group B	75	1.07 + 1.25	

**Table No.2: Distribution of PCOS Group wise**

PCOS	Group		Total
	Group A	Group B	
Oligomenorhea	23	25	48
Weight gain, hirsutism	24	24	48
Increased LH levels	16	14	30
Polycystic ovaries on ultrasound	12	12	24
Total	75	75	150

**Table No.3: Crosstabulation between study groups and monofollicular formation**

Study Group	Monofollicular formation		Total	P-Value
	Yes	No		
Group A	43	32	75	0.005

**DISCUSSION**

This study compared clomiphene citrate and Letrozole in patients with polycystic ovarian syndrome in terms of monomolecular development. In this regard the present randomized control trial was conducted at Gynae unit 1 Outpatient department, Holy Family Hospital Rawalpindi. So one hundred and fifty patients of polycystic ovarian syndrome were included by fulfilling the inclusion and exclusion criteria by using non probability consecutive sampling.

In group A, the mean ± standard deviation of age was found as 28.25 ± 4.43 years and 28.76 ± 4.53 years in group B. The mean ± standard deviation of marriage duration was found as 4.15 ± 1.87 years in group A and 4.20 ± 1.84 years in group B. The mean ± standard deviation of parity was found as 0.72 ± 0.89 in group A and 1.07 + 1.25 in group B.

Razzaq S, et al (2015) described that ovulation related problems have been the most important cause of

infertility among the women of child bearing age reporting in the health care facility. Another study showed that the number of follicles (1.89 ± 0.9 vs 1.18 ± 0.393) and serum estradiol levels (437.5 ± 293.7 pg/mL vs 291.82 ± 59.86 pg/mL) were higher in Group 1, while follicular diameter (20.67 ± 0.970 mm vs. 20.76 ± 0.903 mm) and endometrial thickness (8.5 mm vs.7.4 mm) were similar in both the Groups.<sup>15,16</sup>

In group A, PCOS was diagnosed in 30.67% patients by oligomenorhea, 32% by weight gain, hirsutism, 21.33% by increased LH levels and 16% by ultrasound. In group B, PCOS was diagnosed in 33.33% patients by oligomenorhea, 32% by weight gain, hirsutism, 18.67% by increased LH levels and 16% by ultrasound. Monofollicular formation was observed in 57.33% patients in group A and in group B Monofollicular formation was found in 78.67% patients. In group A, there were 49.33% patients in which primary infertility was detected and 50.67% patients in which secondary infertility was found. In group B, there were 54.67% patients in which primary infertility was detected and 45.33% patients in which secondary infertility was found.

Previous literature showed that nine RCTs compared letrozole with clomiphene citrate (with or without adjuncts) followed by timed intercourse. The birth rate was higher in the letrozole group (OR 1.63, 95% CI 1.31 to 2.03, n=1783, I<sup>2</sup>=3%).<sup>17</sup>

By using t-test, there was no significant difference of age in both groups having p-value = 0.49. There was no significant difference found of marriage duration in both groups having p-value = 0.86. Significant difference of parity was found in both groups having p-value = 0.05.

In another study, the metformin+clomiphene combination compared with gonadotrophins resulted in significantly fewer ovulations and pregnancies clearly highlighting the superior efficacy of gonadotrophins in this regard.

By using chi-square test in present study, there was significant association found between study groups and monofollicular formation. Monofollicular formation was significantly lower in group A having p-value = 0.005. There was not significant association found between age and monofollicular formation having p-value = 0.775. Marriage duration was not significantly associated with monofollicular formation having p-value = 0.085. Parity was not significantly associated with monofollicular formation having p-value = 0.475.<sup>18</sup>

In another research, all the pharmacological and physical treatments used for managing various problems related to ovulation among the patients suffering from PCOS were found equally effective and no treatment was found superior to other.<sup>19</sup>

It was noticed in previous study that clomiphene and letrozole both may be equally effective for managing

the ovulatory problems related to PCOS. Smaller studies have been available regarding one agent efficacious than other but large randomized controlled trials and met analysis should be conducted to reach to some conclusive results.<sup>20</sup>

## CONCLUSION

Letrozole is better as compared to Clomiphene citrate in terms on mono follicular development in patients with PCOS. Effect modifiers have not significant association with mono follicular formation.

### Author's Contribution:

Concept & Design of Study: Maria Tariq  
 Drafting: Hira Suleman, Madiha Khadim  
 Data Analysis: Noreen Tahir  
 Revisiting Critically: Maria Tariq, Hira Suleman  
 Final Approval of version: Maria Tariq

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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