Original Article

# Comparison of Clomiphene Citrate and Letrozole for Ovulation Induction in Polycystic Ovary Syndrome

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## Abstract

Objective: To compare a mean number of mature follicles and endometrial thickness in infertile patients having polycystic ovarian syndrome receiving clomiphene citrate and letrozole.

Study Design: It was a randomized controlled trial.

Place and Duration: This study was carried out at Department of Obstetrics and Gynecology, Combined Military Hospital Muzaffarabad over 6 months from December 2015 to May 2016.

Methodology: This study involved 60 women aged between 18-35 years presenting with infertility and diagnosed of PCOS. Two treatment groups were made by a random division of the patients. Patients of Group-A were given letrozole while clomiphene citrate was given to the patients of Group-B. Mean a number of mature follicles and mean endometrial thickness were the variables used for measuring outcomes in both the groups. An informed written consent was taken from all the patients. A predesigned proforma was used to record patient's demographic details along with case outcome.

Results: The patients had a mean age of 25.75±5.38 years while the mean duration of infertility was 3.17±1.98 years. The mean number of mature follicles (2.83±0.79 vs. 2.10±0.71; p=0.000) was significantly higher but the mean endometrial thickness (7.40±1.87mm vs. 9.17±1.86mm; p=0.001) were significantly lower with letrozole as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups.

Conclusion: This study concludes that in infertile patients with PCOS, letrozole was associated with a significantly higher mean number of mature follicles with significantly lower mean endometrial thickness as compared to clomiphene citrate. Thus letrozole should be preferred in the management of subfertility with PCOS as it would increase the likelihood of pregnancy.

Keywords: Polycystic Ovarian Syndrome, subfertility, Number of Mature Follicles, Endometrial Thickness, Letrozole, Clomiphene Citrate

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## Introduction

Subfertility is a global problem having deep emotional and social repercussions in the affected individuals. After one year's unprotected intercourse, the inability of a couple to conceive is called subfertility. The rate of subfertility is 21.9% in Pakistan.[1] One of the biggest causes of subfertility is PCOS (polycystic ovarian syndrome) which affects 4-7% of women worldwide. It was described five decades ago yet underlying cause

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of the disorder has not been established. It affects approximately 6-10% of women in their reproductive years.[2]

In PCOS patients, the primary cause of subfertility is anovulation. In these patients, for inducing ovulation, CC (clomiphene citrate) is the oldest drug and is considered as the standard of choice. Clomiphene citrate is a highly effective, appropriate and non-expensive agent that is in use since 1963 to induce ovulation.[3] But, it is not successful in all the patients; clomiphene fails to induce ovulation in 15-20% women who are labeled as CC-resistant. Use of clomiphene citrate is reportedly linked with creating other problems like endodermal and anti-estrogenic mucosal changes leading towards a higher rate of miscarriages and abortions in ovulatory women.[3]

So in the quest of better treatment for PCOS patients, another drug letrozole has been recently introduced that belongs to aromatase inhibitor family for inducing ovulation especially in patients of PCOS. The role of letrozole is also impressive in pregnancy that equates to injectable gonadotropins is being cost effective and reported less side effects.[4] It has also been found to have little effect on endometrial thickness, thus promoting fertility rate.[5]

Different studies have been done in other geographical areas with few results in favour of letrozole. This study aims to fill the gap in Pakistani literature related to this serious issue. Hendawy et al. compared clomiphene citrate and letrozole in infertile PCOS women and found that mean number of mature follicle were noticeably more in patients receiving letrozole (2.9±1.77 vs. 1.2±0.9; $p<0.05$) as compared to clomiphene citrate.[6] In another study Scycdoshohadaei et al. didn't observe any substantial differences in mean endometrial thickness between letrozole (6.07±2.76 vs.7.7±4.15mm; $p>0.05$) and clomiphene citrate and established that letrozole was as safe as clomiphene citrate in terms of increase in endometrial thickness.[7] However, Eftekhar et al. claimed that mean endometrial thickness was noticeably higher with letrozole (9.16±1.2 mm vs. 8.3±0.3 mm; $p=0.001$) as compared to clomiphene citrate which is not desirable in these patients.[8]

Due to this controversy in the existing literature and to fill the gap of literature on this issue locally, the purpose of the current study was to compare these two drugs with a hope that the results of the present study would Senable selection of more appropriate treatment for future patients with infertility due to PCOS.

## Methodology

A Randomized controlled trial study was conducted at the Department of Obstetrics & Gynecology at SKBZ/CMH Muzaffarabad over 6 months from December 2015 to May 2016. The sample size was taken as 60 cases (30 in each group) and calculations were made with a level of significance as 5%, the power of test as 80% and expected mean endometrial thickness as 8.39±3.38 in clomiphene citrate group vs. 9.16±1.24 in letrozole group in patients with PCOS.[8] Women aged 18-35 years presenting with subfertility and diagnosed with PCOS were included in this study. Subfertility was labeled as a women failing to conceive after 1-year of marriage with continuous unprotected coitus while PCOS was labeled when two out of the following three criteria were present: oligomenorrhea (interval between periods >35 days), hyperandrogenism (elevated total or free serum testosterone than normal 0.5-2.5nmol/l), polycystic ovaries as seen on ultrasound (if there were ≥12 follicles 2-9 mm in diameter and/or increased ovarian volume ≥10cm3). Female patients had thyroid dysfunction, hyperprolactinemia, diabetes mellitus, congenital adrenal hyperplasia, unexplained infertility and those who had already taken any of these medications previously were excluded from the study. Two treatment groups were made on a random basis. For 5-days, patients in Group-A were given 50 mg of clomiphene citrate twice daily starting from day 2 of the menstrual cycle while patients in Group-B received 5 mg of letrozole daily that also started from 2nd day of menstrual cycle. Follicular monitoring was done by abdominal ultrasonography on days 10, 12, 14, and 16 of the cycle until a mature follicle was detected (≥18 mm by averaging inner two diameters of the follicle on ultrasound). Patients were monitored for endometrial thickness at the day of maturation of follicle. If for 2 consecutive cycles, no mature follicle was observed, it was declared as ovulation failure and no more medication was given to these patients. A written informed consent was signed by each patient. Continuous variables; infertility duration, age, number of follicles and thickness of endometrium have been presented by mean ± SD. Independent samples t-test was applied to compare mean no. of follicles and mean endometrial thickness between the two groups taking p value of ≤0.05 as significant. Confounders for age and subfertility duration was addressed by making strata and independent samples t test was repeated after the stratification was done ($p\leq0.05$).

## Results

The patients had ranged from age 18-35 years with the mean age of 25.75±5.38 years. The majority (63.3%) of the patients were aged between 18-26 years followed by 27-35 years. Duration of infertility ranged from 1 to 9 years with a mean of 3.17±1.98 years. 40 (66.7%) patients had infertility for 1-3 years followed by patients in whom duration of infertility ranged between 4-9 years [20(33.3%)]. No statistically significant difference in both the groups was found in terms of mean infertility duration and age as shown in Table I.

The mean number of mature follicles was noticeably higher with letrozole (2.83±0.79) as compared to clomiphene citrate (2.10±0.71) and this difference was significant (p=0.000) across all ages and duration of infertility groups as given in Table II.

The mean endometrial thickness was significantly lower with letrozole as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups as shown in Table III.

## Discussion

In women with PCOS anovulatory infertility is the chief cause of ovulatory dysfunction.[9] Despite having high recruitment of follicles in PCOs, there is a stoppage in growth upon reaching the diameter of 5-8 mm.[10] With

**Table I: Demographic characteristics**

| Characteristics | Participants n=60 | Letrozole n=30 | Clomiphene Citrate n=30 | P value |
|---|---|---|---|---|
| **Age (years)** | 25.75±5.38 | 25.77±5.40 | 25.73±5.45 | 0.981 |
| **18-26 years** | 38 (63.3%) | 18 (60.0%) | 20 (66.7%) | |
| **27-35 years** | 22 (36.7%) | 12 (40.0%) | 10 (33.3%) | 0.592 |
| **Duration of Infertility (years)** | 3.17±1.98 | 3.27±2.13 | 3.07±1.86 | 0.700 |
| **1-3 years** | 40 (66.7%) | 19 (63.3%) | 21 (70.0%) | |
| **4-9 years** | 20 (33.3%) | 11 (36.7%) | 9 (30.0%) | 0.584 |
| Independent sample t-test and chi-square test, observed difference was statistically insignificant | | | | |

**Table II: Comparison of Mean Number of Mature Follicles**

| | Mean Number of Mature Follicles | | |
|---|---|---|---|
| **Characteristics** | **Letrozole (n=30)** | **Clomiphene Citrate(n=30)** | **P value** |
| Overall | 2.83±0.79 | 2.10±0.71 | 0.000* |
| **Age Groups** | | | |
| • 18-26 years | 2.78±0.88 | 2.10±0.64 | 0.010* |
| • 27-35 years | 2.92±0.67 | 2.10±0.88 | 0.022* |
| **Duration of Infertility Groups** | | | |
| • 1-3 years | 2.84±0.83 | 2.14±0.73 | 0.007* |
| • 4-9 years | 2.82±0.75 | 2.00±0.71 | 0.023* |
| Independent sample t-test, * observed difference was statistically significant | | | |

**Table III: Comparison of Mean Endometrial Thickness (mm)**

| | Mean Endometrial Thickness (mm) | | |
|---|---|---|---|
| **Characteristics** | **Letrozole (n=30)** | **Clomiphene Citrate (n=30)** | **P value** |
| Overall | 7.40±1.87 | 9.17±1.86 | 0.001* |
| Age Groups | | | |
| 18-26 years | 7.45±1.85 | 9.17±2.07 | 0.010* |
| 27-35 years | 7.30±2.00 | 9.17±1.59 | 0.024* |
| **Duration of Infertility Groups** | | | |
| 1-3 years | 7.48±2.04 | 9.11±1.99 | 0.015* |
| 4-9 years | 7.22±1.48 | 9.27±1.68 | 0.010* |
| Independent sample t-test, * observed difference was statistically significant | | | |

passing time, a number of hypotheses were put forth as the primary cause of ovulatory dysfunction of PCOS.

Common observations of over production of androgen by theca of PCOS ovaries led to the suggestion of a causative mechanism for anovulation; but there are questions on the rationality of this assumption that there is excessive production of androgen by theca cells of PCOS in ovulatory women.[11] In PCOS patients, recently insulin resistance has been valued as a chief metabolic defect. An inverse correlation between the sensitivity of insulin and the number of cycles per annum are first findings made by numerous studies to prove a link between insulin resistance and anovulation.[12] For inducing ovulation, In women with PCOS, the first treatment of choice is clomiphene citrate.[13,14] The drug is a modulator of estrogen receptors. Oral administration, lower costs and reduced sides effects (visual disturbance, headache, flushing and discomfort of the abdomen) are the benefits of using clomiphene citrate. Development of monofollicuar induction is also reported[14] and the rate of multiple gestations is also very low (2 to 13%).[15] Over last few decades, letrozole belonging to aromatase inhibitor family was introduced as a new choice for inducing ovulation, particularly in PCOS patients. The efficiency of letrozole equates to injectable gonadotropins in terms of pregnancy rate yet with low cost and less side effects.[4] The administration of letrozole for 5 or 10 days at a dose of 5 or 7.5 mg/day displayed clinical pregnancy rates similar to gonadotropins.[16]

In the present study, the mean age of the patients was 25.75±5.38 years. Seyedoshohadaei et al. reported the similar mean age of 24.72±4.66 years among Iranian such women [8]. Eid et al. (2014), Fouda et al. (2011) and Badaway et al. (2009) observed similar mean age of 25.6±4.34 years, 26.68±3.51 years, and 25.1±2.11 years respectively in Egyptian such patients.[17,18,19] Hameed et al. (2012) reported a relatively higher mean age of 29±4.5 years in patients of PCOS presenting with infertility at PAF Hospital, Lahore Pakistan.[20]

We observed that the majority (63.3%) of the patients were aged between 18-26 years followed by 36.7% patients aged between 27-35 years. Razzaq et al. (2015) also observed 18-26 years being the most frequent (63.21%) age group among such patients presenting at Bahawal Victoria Hospital, Bahawalpur.[21]

Mean duration of infertility agreed with Fouda et al. (3.69±1.88 years) and Hameed et al. (3.5±1.1 years) reported the similar mean duration of infertility at presentation among such patients.[18,20] Hameed et al. also reported 1-3 years duration of infertility is the most frequent group observed among such patients presenting at CMH Peshawar.[20]

This study has observed the mean number of mature follicles as significantly higher with letrozole (2.83±0.79 vs. 2.10±0.71; p=0.000) as compared to clomiphene citrate. This was in agreement with Fouda et al. who also observed that mean number of mature follicles with letrozole was higher as compared to clomiphene citrate (2.24±0.80 vs. 2.13±0.76). However, the difference was not statistically significant in their series (p=0.456) which can be due to selection bias where they included patients undergoing superovulation and intrauterine insemination (IUI).[18]

It is also observed in this study that letrozole was associated with significantly lower mean endometrial thickness (7.40±1.87mm vs. 9.17±1.86mm; p=0.001) as compared to clomiphene citrate. Same results were observed in the previously published research by Scycdoshohadaei et al. who also observed the similar but insignificant difference in the mean endometrial thickness between letrozole (6.07±2.76 vs. 7.7±4.15mm; p>0.05) and clomiphene citrate.[7]

The present study is first of its kind in local population and has found that in infertile patients with PCOS, letrozole was associated with a significantly higher mean number of mature follicles and lower mean endometrial thickness as compared to clomiphene citrate. In the light of this evidence, letrozole appears a more effective treatment option for ovulation induction and should be preferred in future practice.

This study finds its limitations in evaluating the side effects of treatment drug that needs further work before it is administered properly in routine PCOS patients.

## Conclusion

The observation showed that treating subfertility of women with PCOS, letrozole was associated with a significantly higher mean number of mature follicles and lower mean endometrial thickness as compared to clomiphene citrate. Thus, letrozole could be a preferred treatment in the management of subfertility with PCOS with PCOS as it would increase the likelihood of pregnancy.

## References

1. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility. Pak J Med Sci. 2015;31:694-9.
2. Kl-Gharib MN, Mahfouz AG, Farahat MA. Comparison of letrozole versus tamoxifen effects in clomiphen citrate resistant

women with polycystic ovarian syndrome. J Reprod Infertil 2015;16:30-5.
3. Ghomian N, Khosravi A, Mousavifar N. A randomized clinical trial on comparing the cycle characteristics of two different initiation days of letrozole treatment in clomiphene citrate resistant pcos patients in iui cycles. Int J Fertil Steril 2015;9:17-26.
4. Hajishafiha M, Dehghan M, Kiarang N, Sadegh-Asadi N, Shayegh SN, Ghasemi-Rad M. Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug Des Devel Ther. 2013;7:1427-31.
5. Foroozanfard F, Saberi H, Moraveji SA, Bazarganipour F. Pregnancy rate following luteal phase support in Iranian women with polycystic ovarian syndrome. Int J Fertil Steril 2014;8:235-42.
6. Hendawy SF, Samaha HE, Elkholy MF. Letrozole versus clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome undergoing intrauterine insemination. Clin Med Insights Reprod Health. 2011;5:11-6.
7. Seyedoshohadaei F, Zandvakily F» Shahgeibi S. Comparison of the effectiveness of clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to isolated unovulation. Iran J Reprod Med. 2012;10:531-6.
8. Eftekhar M, Mohammadian F, Davar R, Pourmasumi S. Comparison of pregnancy outcome after letrozole versus clomiphene treatment for mild ovarian stimulation protocol in poor responders. Iran J Reprod Med 2014;12:725-30.
9. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Update 2008;14(4):367-78.
10. Padmanabhan V, Veiga-Lopez A. Sheep models of polycystic ovary syndrome phenotype. Mol Cell Endocrinol. 2013;373(1-2):8-20.
11. Joseph-Horne R, Mason H, Batty S, White D, Hillier S, Urquhart M, et al. Luteal phase progesterone excretion in ovulatory women with polycystic ovaries. Hum Reprod 2002;17(6):1459-63.
12. Robinson S, Kiddy D, Gelding SV, Willis D, Niththyananthan R, Bush A, et al. The relationship of insulin insensitivity to menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin Endocrinol (Oxf). 1993;39(3):351-5.
13. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008) Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod. 2013;23(3):462-77.
14. Perales-Puchalt A, Legro RS. Ovulation induction in women with polycystic ovary syndrome. Steroids. 2013;78(8):767-72.12
15. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-estrogens for ovulation induction in PCOS. Cochrane Database Syst Rev. 2009;4:CD002249.
16. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014;2:CD010287.
17. Eid SM, Shakweer MM. Effect of late luteal phase clomiphene citrate on ovulation induction and endometrial blood flow in patients with polycystic ovary syndrome. Clin Med Diagnostics. 2014;4(4):65-70.
18. Fouda UM, Sayed AM. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized controlled trial. Reprod Biol Endocrinol. 2011;9:84.
19. Badawy A, Inany H, Mosbah A, Abulatta M. Luteal phase clomiphene citrate for ovulation induction in women with polycystic ovary syndrome: a novel protocol. Fertil Steril. 2009;91(3):838-41.
20. Hameed N, Ali MA. Laparoscopic ovarian drilling for polycystic ovarian syndrome: treatment outcome. J Ayub Med Coll Abbott. 2012;24(4):90-2.
21. Razzaq S, Rasheed S, Pansota MS, Fatima N. Efficacy in term of orally administered letrozole versus clomiphene citrate in anovulatory infertility. Gomal J Med Sci. 2015;13:15-8.