To Compare the Efficacy of Clomid and Letrozole in Polycystic Ovary Syndrome

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Abstract

Background: The most common cause of medically treatable infertility is polycystic ovarian syndrome (PCOS). Anovulation is a major cause of infertility in patients of PCOS. Clomiphene citrate (CC) is known as one of the oldest drugs that has remained the standard choice for ovulation induction in such patients. However, about 15-20% of women don't ovulate on CC and are labelled as CC-resistant group. Another drug Letrozole has been recently introduced and is claimed to be superior to clomiphene citrate in ovulation induction. However, there was controversy in the existing literature and there was no such local published material available which necessitated the present study. The objective of this study was to compare mean number of mature follicle and endometrial thickness in infertile patients with polycystic ovarian syndrome receiving clomiphene citrate and letrozole.

Methods: It was a randomized controlled trial conducted at Department of Obs & Gynae at SKBZ/CMH Muzaffarabad from 02/12/2015 to 01/06/2016.This study involved 60 women aged between 18-35 years presenting with infertility and diagnosed with PCOS. These patients were randomly divided into two treatment groups. Patients in Group-A received Letrozole while patients in Group-B received clomiphene citrate. Outcome variable were mean endometrial thickness and mean number of mature follicles. A written informed consent was taken from each patient.

Results: The age of the patients ranged from 18 years to 35 years with a mean of 25.75±5.38 years. Majority (63.3%) of the patients were aged between 18-26 years followed by 36.7% patients aged between 27-35 years. Duration of infertility ranged from 1 year to 9 years with a mean of 3.17±1.98 years. 40 (66.7%) patients had infertility for 1-3 years followed by 20 (33.3%) patients in whom duration of infertility ranged between 4-9 years. There was no statistically significant difference between the two groups in terms of mean age (p=0.981), mean duration of infertility (p=0.700) and age (p=0.592) and duration of infertility (p=0.584) groups distribution. The mean number of mature follicles was significantly higher with letrozole (2.83±0.79 vs. 2.10±0.71; p=0.000) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups. The mean endometrial thickness was significantly higher with letrozole (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups.

Conclusion: In infertile patients with PCOS, letrozole was associated with significantly higher mean number of mature follicles (2.83±0.79 vs. 2.10±0.71; p=0.000) and mean endometrial thickness (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups.

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

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INTRODUCTION

Infertility is a worldwide problem which has profound social and emotional implications for the affected individuals. Infertility is defined as inability of a couple to conceive after one year of unprotected intercourse. The prevalence of infertility in Pakistan is 21.9%[1]. The most common cause of medically treatable infertility is polycystic ovarian syndrome (PCOS). PCOS affects 4- 7% of women worldwide. It was described more than half a century ago but still the underlying cause of this disorder is unknown. It affects approximately 6-10% of women in their reproductive years[2].

Anovulation is a major cause of infertility in patients of PCOS. Clomiphene citrate (CC) is known as one of the oldest drugs that has remained the standard choice for ovulation induction. CC. has been an appropriate, non-expensive and highly effective agent for inducing ovulation since 1963. However, it certainly has not been successful in all patients; about 15-20% of women do not ovulate on CC, labeled as CC-resistant group. There are also other problems reported about CC, such as the anti-estrogenic mucosal and endometrial changes that lead to higher rate of abortion and miscarriage in ovulatory women[3].

So in the search of better treatment for PCOS patients, another drug, Letrozole has been recently introduced. Letrozole belonging to aromatase inhibitor family has been introduced as a new choice for ovulation induction in the past decade, especially in PCOS patients. Letrozole also seems to be very efficient in pregnancy rates, equivalent to injectable gonadotropins, at lower cost and with fewer adverse effects[4]. It is also found having little effect on endometrial thickness, thus promoting fertility rate[5].

Hendawy SF and colleagues conducted a trial and compared Letrozole and CC in infertile women with PCOS and they found that mean number of mature follicle in patients receiving Letrozole were 1.2 ± 0.9 versus 2.9 ± 1.77 in patients receiving CC (P= <0.05)[6]. Eftekhar M and colleagues also compared Letrozole and CC and they found that endometrial thickness was 9.16 ± 1.2 mm vs. 8.3 ± 0.3 mm (P = 0.001) in two groups respectively[7]. In another study by Scycdoshohadaei F, endometrial thickness was found to be 7.7 ± 4.15mm in CC group while 6.07 ± 2.76 mm in Letrozole group[8].

As controversy in the literature exists[6,7,8] that which drug is better for mean no of mature follicle and endometrial thickness for PCOS, therefore I wanted to conduct this study. This study helped us to find better drug for patients with PCOS in our population.

MATERIALS AND METHODS

It's a randomized controlled trial conducted at Department of Obs. & Gynae. at SKBZ/CMH Muzaffarabad from 02/12/2015 to 01/06/2016.Sample size of 60 cases (30 in each group) was calculated with 80% power of test, 5% level of significance and taking expected mean level of endometrial thickness in both groups i.e. 8.39±3.38 in Clomiphene Citrate group vs. 9.16±1.24 in Letrozole group in patients with PCOS[7] pooled SD 0.81. Patients were selected by Non-Probability, Consecutive Sampling.

All the infertile women of having PCOS (as described in operational definition) aged 17-35 years were included in the study. Assessed by history, examination and laboratory tests patients having diabetes mellitus, thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, those with unexplained infertility or patients who had already taken any of these medications previously were excluded from this study.

Approval from Ethical Review Board of the hospital was obtained. The patients meeting the inclusion criteria were included in the study through OPD. Patients were divided by lottery method into two groups: group A (Clomiphene Citrate), group B (Letrozole). Informed consent for inclusion in the study was taken from each patient. They were assured regarding confidentiality and expertise of the physician and were educated for an anticipated better outcome. Patients in group A received 150 mg of CC daily while patients in group B received 7.5 mg of letrozole daily for 5 days starting from day 3 of the 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 (as defined in operational definitions). 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 in these patients. All data was recorded on the proforma (attached).

All the collected data was entered and analyzed through SPSS version 21. Numerical variables; age, duration of infertility, number of follicles and endometrial thickness have been presented by mean ±SD. Independent sample t-test has been applied to compare mean no. of follicles and mean endometrial thickness between the two groups taking p value ≤ 0.05 as significant. Data has been stratified for age and duration of infertility to address effect modifiers. Post-stratification independent sample test has been applied taking p value ≤ 0.05 as significant.

RESULTS

The age of the patients ranged from 18 years to 35 years with a mean of 25.75±5.38 years.

Majority (63.3%) of the patients were aged between 18-26 years followed by 36.7% patients aged between 27-35 years. Duration of infertility ranged from 1 year to 9 years with a mean of 3.17±1.98 years. 40 (66.7%) patients had infertility for 1-3 years followed by 20 (33.3%) patients in whom duration of infertility ranged between 4-9 years. There was no statistically significant difference between the two groups in terms of mean age (p=0.981), mean duration of infertility (p=0.700) and age (p=0.592) and duration of infertility (p=0.584) groups distribution as shown in Table 9.1.

The mean number of mature follicles was significantly higher with letrozole (2.83±0.79 vs. 2.10±0.71; p=0.000) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups as shown in Table 9.2.

The mean endometrial thickness was significantly higher with letrozole (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups as shown in Table 9.3.

Table Error! No text of specified style in document.**.1 Baseline Characteristics of Study Sample**

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%)**	**0.592**
• 27-35 years	22 (36.7%)	**12 (40.0%)**	**10 (33.3%)**	
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%)**	**0.584**
• 4-9 years	20 (33.3%)	**11 (36.7%)**	**9 (30.0%)**	

Independent sample t-test and chi-square test, observed difference was statistically insignificant

Table Error! No text of specified style in document.**.2 Comparison of Mean Number of Mature Follicles**

Characteristics	**Mean Number of Mature Follicles**		**P value**
	Letrozole n=30	**Clomiphene Citrate n=30**	
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±	2.14±0.73	0.00

• 4-9 years	0.83 2.82± 0.75	2.00±0.71	7* 0.02 3*

Independent sample t-test,
* observed difference was statistically significant

Table Error! No text of specified style in document.**.3 Comparison of Mean Endometrial Thickness (mm)**

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

Independent sample t-test,
* observed difference was statistically significant

DISCUSSION

Infertility is a worldwide problem which has profound social and emotional implications for the affected individuals[1]. The most common cause of medically treatable infertility is polycystic ovarian syndrome (PCOS)[2]. Anovulation is a major cause of infertility in patients of PCOS. Clomiphene citrate (CC) is known as one of the oldest drugs that has remained the standard choice for ovulation induction. However, about 15-20% of women do not ovulate on CC and are labelled as CC-resistant group[3]. Another drug Letrozole has been recently introduced and is claimed to be superior to clomiphene citrate[6,7,8]. However, there was controversy in the existing literature and there was no such local published material necessitating the present study.

The objective of this study was to compare mean number of mature follicle and endometrial thickness in infertile patients with polycystic ovarian syndrome receiving clomiphene citrate and letrozole. It was a randomized controlled trial conducted at Department of Obs & Gynae at SKBZ/CMH Muzaffarabad over 6 months after the approval of synopsis from 02/12/2015 to 01/06/2016.

This study involved 60 women aged between 18-35 years presenting with infertility and diagnosed of PCOS. These patients were randomly divided into two treatment groups. Patients in Group-A received Letrozole while patients in Group-B received clomiphene citrate. Outcome variable were mean endometrial thickness and mean number of mature

follicles. A written informed consent was taken from each patient.

The age of the patients ranged from 18 years to 35 years with a mean of 25.75±5.38 years. Seyedoshohadaei et al. reported similar mean age of 24.72±4.66 years among Irani 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, 26.68±3.51, and 25.1±2.11 years respectively in Egyptian such patients[9,10,11]. 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[12]. 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[13].

Duration of infertility ranged from 1 year to 9 years with a mean of 3.17±1.98 years. 40 (66.7%) patients had infertility for 1-3 years followed by 20 (33.3%) patients in whom duration of infertility ranged between 4-9 years. Fouda et al. (3.69±1.88 years) and Hameed et al. (3.5±1.1 years) reported similar mean duration of infertility at presentation among such patients[10,12]. Hameed et al. also reported 1-3 years being the most frequent duration group observed among such patients presenting at CMH Peshawar[12].

There was no statistically significant difference between the two groups in terms of mean age (p=0.981), mean duration of infertility (p=0.700) and age (p=0.592) and duration of infertility (p=0.584) groups distribution. Thus randomization was effective and there was no inherent bias among the study groups.

The mean number of mature follicles was significantly higher with letrozole (2.83±0.79 vs. 2.10±0.71; p=0.000) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups. Our results match with those of 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 insignificant in their series (p=0.456) which can be due to selection bias where they included patients undergoing superovulation and intrauterine insemination (IUI)[10].

The mean endometrial thickness was significantly higher with letrozole (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups. Our results are in line with the previously published research by Eftekhar et al. (9.16±1.2mm) and Seyedoshohadaei et al. (7.7±4.15mm) who observed similar mean endometrial thickness with letrozole and clomiphene citrate respectively[7,8].

The present study is first of its kind in local population and has found that in infertile patients with PCOS, letrozole was associated with significantly higher mean number of mature follicles (2.83±0.79 vs. 2.10±0.71; p=0.000) and mean endometrial thickness (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups. In the light of this evidence, letrozole appears a more effective treatment option and should be used in future practice.

There is a strong limitation to the present study and that is we didn't consider the treatment side effects which are also important and should be considered in future studies.

CONCLUSION

In infertile patients with PCOS, letrozole was associated with significantly higher mean number of mature follicles (2.83±0.79 vs. 2.10±0.71; p=0.000) and mean endometrial thickness (9.17±1.86mm vs. 7.40±1.87mm; p=0.001) as compared to clomiphene citrate and this difference was significant across all age and duration of infertility groups.

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