

Research Article**Comparison of efficacy between letrozole and clomiphene citrate in an ovulatory infertile women****¹Sabahat Fatima, ²Duaa Akhter****and ³Muhammad Haseeb ur Rehman**¹Ex-House Officer, Nishtar Hospital Multan²Woman Medical Officer, BHU Ain Wahin³Medical Officer, BHU 339/TDA Tehsil & District Layyah**ABSTRACT****Objectives:** To compare the efficacy between letrozole and clomiphene citrate in an ovulatory infertile woman.**Material and methods:** This randomized controlled trial was conducted at Department of Obstetrics and Gynecology Nishtar Hospital, Multan from November 2016 to May 2017. A total of 224 patients, 18 to 40 years of age with an ovulatory infertility were included.**Results:** The mean age of women in group A was 26.72 ± 6.02 years and in group B was 26.87 ± 6.33 years. Majority of the patients 148 (66.07%) were between 18 to 30 years of age. Mean duration of infertility was 3.47 ± 2.21 years. The mean duration of infertility in group A was 3.23 ± 2.19 years and in group B was 3.68 ± 2.34 years. Effectiveness of Group A (clomiphene citrate group) was 19 (16.96%) while in Group B (letrozole group) was 37 (33.04%) (p-value = 0.005).**Conclusion:** This study concluded that letrozole is better and more efficacious in terms of achieving pregnancy in the treatment of an ovulatory infertility as compared to the clomiphene citrate.**Keywords:** An ovulatory infertility, letrozole, clomiphene citrate, pregnancy rate.**INTRODUCTION**

Ovulation is the result of a maturation process that occurs in the hypothalamic-pituitary-ovarian (HPO) axis and is orchestrated by a neuroendocrine cascade terminating in the ovaries¹. Ovulation dysfunction is one of the most common causes of reproductive failure in infertile couples. The prevalence of this disorder in infertile women is about 30 to 40%.²

The HPO axis is the target of first line ovulation-induction therapy^{3,4} which includes oral fertility medication i.e, clomiphene citrate or letrozole are the two most common, can be augmented by hCG. Injectable fertility medications i.e, Gonal-F, Follistim, Menopuror, Repronex can be used with

intrauterine insemination or in-vitro fertilization. But, the oral fertility drugs are the most commonly used therapy for ovarian dysfunction worldwide.^{4,5}

Clomiphene citrate is a selective estrogen-receptor modulator (SERM) that antagonizes the negative feedback of estrogen at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin.⁶ Clomiphene has drawbacks, including its overall poor efficacy, a relatively high multiple-pregnancy rate and an undesirable side-effect profile, including mood changes and hot flushes.⁶ Letrozole is a non-steroidal aromatase inhibitor, which blocks

estrogen synthesis by the conversion of androgens through the activity of the aromatase enzyme thus, directly affect hypothalamic–pituitary–ovarian function and increase pregnancy rates by ovarian stimulation. Potential advantages of aromatase inhibitors over SERM include a more physiologic hormonal stimulation of the endometrium, a lower multiple-pregnancy rate, a better side-effect profile with fewer vasomotor and mood symptoms, and more rapid clearance.^{6,7}

The aim of this study was to compare the effectiveness of Letrozole and Clomiphene for ovulation induction in an ovulatory infertility so that some practical recommendations could be made to achieve maximum number of pregnancies in an ovulatory infertile women with more efficacious treatment regime.

OPERATIONAL DEFINITION

An ovulatory Infertility: was defined as the patients having contraceptive free sexual intercourse for >1 year and not getting pregnancy despite of having normal pelvic ultrasonography, bilateral normal tubal patency on hysterosalpingography and normal male factor.

Effectiveness: was measured in terms of occurrence of pregnancy by measuring β -HCG at day 5 after the first missed menstrual period;

Effectiveness was deemed as yes if there was occurrence of pregnancy β -HCG levels of ≥ 5 mIU/ml at day 5 after the first missed menstrual period, otherwise taken as no.

MATERIALS & METHODS

Randomized controlled trial was conducted at Department of Obstetrics & Gynecology, Nishtar Hospital, Multan from November 2016 to May 2017. A total of 224 patients, 18 to 40 years of age with an ovulatory infertility were included.

Patients with history of pelvic surgery, hypothyroidism and patients with hyperprolactinemia were excluded from the study. Patients were randomly divided into two groups A and B. Group A contained patients who were advised clomiphene citrate orally once a day for 5 days (3-7) of menstrual cycle for up to 5

menstrual cycles and group B contained patients who were advised 2.5 mg letrozole orally once a day on days 3-7 of menstrual cycle for upto 5 menstrual cycles. All patients of both groups were evaluated after completion of each cycle to see the occurrence of pregnancy which was confirmed by measuring β -HCG at day 5 after the first missed menstrual period and effectiveness of each group was noted as per-operational definition. This all data was recorded on a specially designed performa.

The collected information was analyzed by computer software SPSS 20.0. Mean and standard deviation were calculated for quantitative variables i.e. age and duration of infertility. Frequency and percentage were calculated for qualitative variables i.e. effectiveness (yes/no). Chi Square test was applied to compare effectiveness in both groups. Effect modifiers like age and duration of infertility were controlled through stratifications and post stratification chi Square was applied to see the effect of these on effectiveness. P value ≤ 0.05 was considered significant.

RESULTS

Age range in this study was from 18 to 40 years with mean age of 26.76 ± 6.19 years. The mean age of women in group A was 26.72 ± 6.02 years and in group B was 26.87 ± 6.33 years. Mean duration of infertility was 3.47 ± 2.21 years. The mean duration of infertility in group A was 3.23 ± 2.19 years and in group B was 3.68 ± 2.34 years.

Effectiveness of Group A (clomiphene citrate group) was 19 (16.96%) while in Group B (letrozole group) was 37 (33.04%) (p-value = 0.005). (Table 1)

Patients were divided into two age group i.e. age group 18-30 years and age group 31-40 years. In age group 18-30 years, efficacy to treatment was noted in 10 (13.70%) patients of group A and in 24 (32.0%) patients of group B. statistically significant (P = 0.008) difference of efficacy between the both groups was noted. In age group 31-40 years, efficacy of treatment was noted in 09

(23.08%) patients of group A and in 13 (35.14%) patients of group B. Difference of efficacy between the both groups was statistically insignificant with p value 0.247. (Table 2)

In patients with duration of infertility <5 years, efficacy of treatment was noted in 12 (16.90%) patients of group A and in 26 (37.68%) patients of group B. difference of efficacy rate between the

both groups was statistically significant with p value 0.006. In patients with >5 years duration of infertility, efficacy of treatment was noted in 07 (17.07%) patients and in 11 (25.58%) patients of group A and B. But the difference of efficacy rate between the both groups was statistically insignificant with p value 0.342. (Table 3)

Table 1: Comparison of efficacy

| Group | Efficacy | | P value |
|-------|-------------|-------------|--------------|
| | Yes | No | |
| A | 19 (16.96%) | 93 (83.04%) | 0.005 |
| B | 37 (33.04%) | 75 (66.96%) | |

Table 2: Comparison between effectiveness of both groups according to age.

| Age of patients (years) | Group A (n=112) | | Group B (n=112) | | P-value |
|-------------------------|-----------------|-------------|-----------------|-------------|--------------|
| | effectiveness | | effectiveness | | |
| | yes | no | yes | no | |
| 18-30 years | 10 (13.70%) | 63 (86.30%) | 24 (32.0%) | 51 (68.0%) | 0.008 |
| 31-40 years | 09 (23.08%) | 30 (76.92%) | 13 (35.14%) | 24 (64.86%) | 0.247 |

Table 3: Comparison between effectiveness of both groups according to duration of infertility

| Duration of infertility | Group A (n=112) | | Group B (n=112) | | P-value |
|-------------------------|-----------------|-------------|-----------------|-------------|--------------|
| | effectiveness | | effectiveness | | |
| | yes | no | yes | no | |
| < 5 years | 12 (16.90%) | 59 (83.10%) | 26 (37.68%) | 43 (62.32%) | 0.006 |
| >5 years | 07 (17.07%) | 34 (82.93%) | 11 (25.58%) | 32 (74.42%) | 0.342 |

DISCUSSION

The purpose of the study was to compare the effectiveness (in terms of achieving pregnancy) of letrozole vs clomiphene citrate in an ovulatory infertile women. Age range in this study was from 18 to 40 years with mean age of 26.76 ± 6.19 years. The mean age of women in group A was 26.72 ± 6.02 years and in group B was 26.87 ± 6.33 years. Majority of the patients 148 (66.07%) were between 18 to 30 years of age. Effectiveness of Group A (clomiphene citrate group) was 19 (16.96%) while in Group B (letrozole group) was 37 (33.04%) (p-value = 0.005). The study by Ibrahim MI⁸ showed pregnancy rate of 23.07% in the letrozole group and 10.68% in the clomiphene group.

In a study⁹ Group A received clomiphene, Group B received tamoxifen, Group C received letrozole. Overall ovulation rate was 60 (73.4%), this rate in group A (clomiphene) was 39 (78%), in group B

(tamoxifen) it was 24 (68%) and in group C (letrozole) was 37 (74%). Pregnancy rate in groups A, B and C were, 32 (64%), 20 (40%), and 25 (50%) respectively.

Atay V et al¹⁰ reported that pregnancy rate was significantly higher in the letrozole group as compared to the clomiphene group. Bayar U et al¹¹ reported no significant difference in pregnancy rate between clomiphene group and letrozole group. In a study by Kar et al⁶, ovulation rate was 60.78% with clomiphene citrate and 73.08% with letrozole, which was not statistically significant (p=0.39).

In his study Roy et al² has compared letrozole versus clomiphene citrate in achieving pregnancy and has found efficacy significantly higher in letrozole group (43.8%) compared with clomiphene citrate group (26.4%). In another study by Hussain et al¹², pregnancy rate found was notably higher in the Letrozole group compared to the Clomiphene citrate group with 25.3% and

16.0% respectively. In another study, pregnancy rate per cycle was 11.9 % (7/59) in the letrozole group and 8.8 % (6/68) in the CC group.¹³

CONCLUSION

This study concludes that letrozole is better and more efficacious in terms of achieving pregnancy in the treatment of an ovulatory infertility as compared to the clomiphene citrate. So, we recommend that letrozole should be used as a first line therapy in an ovulatory infertile women in order to achieve maximum number of pregnancies.

REFERENCES

1. El-Gharib MN, Mahfouz AE, Farahat MA. Comparison of letrozole versus tamoxifen effects in clomiphene citrate resistant women with polycystic ovarian syndrome. *J Reprod Infertil*. 2015;16:30-5.
2. Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, et al. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *J Hum Reprod Sci*. 2012;5:20-5.
3. Eftekhari 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.
4. Sakhavar N, Kaveh M, Sadegi K. The impact of letrozole versus clomiphene citrate on uterine blood flow in patients with unexplained infertility. *J Family Reprod Health*. 2014;8:1-5.
5. Banerjee Ray P, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. *Arch Gynecol Obstet*. 2012;285:873-7.
6. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: a prospective randomized trial. *J Hum Reprod Sci*. 2012;5:262-5.
7. Kamath MS, George K. Letrozole or clomiphene citrate as first line for an ovulatory infertility: a debate. *Reprod Biol Endocrinol*. 2011;9:86.
8. Ibrahim MI, Moustafa RA, Abdel-Azeem AA. Letrozole versus clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. *Arch Gynecol Obstet*. 2012;286:1581-7.
9. 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 Nov; 10(6): 531-536.
10. Atay V, Cam C, Muhcu M, Cam M, Karateke A: Comparison of Letrozole and Clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *J Int Med Res*. 2006, 34: 73-76.
11. Bayar U, Basavan M, Coskun A, Gezer S: Use of an aromatase inhibitors in Patient with polycystic ovary syndrome: a prospective randomized trial. *Fertil Steril*. 2006, 86: 1447-1451.
12. Hussain NHN, Ismail M, Zain MM, Yeu PC, Ramli R, Mohammad WMZW. Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. *Open J Obstet Gynecol* 2013;3:11-7.
13. Parihar M, Gada D, Paul PG, Bhowmik S. Letrozole versus Clomiphene Citrate in Patients with An ovulatory Infertility. *South Asian Federation Obstet Gynecol*. 2009;1(1):19-23.