ORIGINAL ARTICLE

# EFFICACY OF LETROZOLE VERSUS CLOMIPHENE CITRATE IN ANOVULATORY INFERTILITY

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## ABSTRACT

**Background:** Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility. Polycystic ovarian syndrome remains one of its leading causes. This trial was done to see the efficacy of letrozole and clomiphene citrate in anovulatory infertility.

**Material & Methods:** This randomized controlled trial was conducted at Obstetrics & Gynaecology Unit, Bahawal Victoria Hospital, Bahawalpur, from January 2012 to June 2014. A total of 212 patients of age 20 to 38 years with anovulatory infertility were included in the study. Patients with other causes of infertility, history of previous genital tract surgery and drugs likely to interfere with ovulation were excluded. These patients were placed randomly into Group A (clomiphene citrate) and Group B (letrozole), by using lottery method. Outcome variables like efficacy i.e. occurrence of pregnancy, were noted.

**Results:** The mean age of women in group A was 26.67±4.23 and in group B 26.24±4.18 years. The mean duration since marriage in group A was 4.06±1.95 years and in group B 4.26±2.12 years. Efficacy of clomiphene citrate was 10.38% while that of letrozole was 21.70% (p=0.02).

**Conclusion:** Letrozole is more effective than clomiphene citrate in the treatment of anovulatory infertility.

**KEYWORDS:** Female infertility; Pregnancy; Aromatase inhibitors; Compliance.

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## INTRODUCTION

Ovulation is the central event in the reproduction cycle. Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility. Polycystic ovarian syndrome (PCOS) with abnormalities in the metabolism of androgens and estrogen and in the control of androgen production, remains one of its leading causes.[1] Using the Rotterdam criteria a clinical diagnosis of PCOS is easily reached and most often treatment can be initiated following a few basic investigations and exclusion of the male factor problem.[2]

For more than four decades, clomiphene citrate has been the first line therapy for induction of ovulation in women with anovulatory infertility and for superovulation in couples with unexplained infertility, mild endometriosis and mild male factor of infertility for a variety of reasons. It is orally administered, has few side effects, is easily available and is inexpensive.[3] Although ovulation rates are in the range of 70-80% the actual pregnancy rates are significantly lower at around 30-40%.[4] It could be used as a superovulation regimen for timed intercourse or intrauterine insemination (IUI) cycles, when favorably combined with exogenous gonadotropins.[5] Because of its long half-life (two weeks), clomiphene citrate accumulates in the body and may have a negative effect on the quality and quantity of cervical mucus, endometrial development, which may cause implantation failure, luteal phase defects and significant thinning of the endometrium. Clomiphene citrate resistance together with side effects like multifollicular development and cyst formation are areas of concern. The desire for an effective alternative persists.[6]

Letrozole, an aromatase inhibitor, was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance.[7] Letrozole has found acceptance in various clinical situations and the indications for use have expanded.[8]

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In contrast to clomiphene, letrozole at the customary dose of 2.5 mg elicits a monofollicular response and does not adversely affect either the endometrium or the cervical mucus, due to an absence of a peripheral estrogen receptor blockage.[9] The often asked question of whether it is better than clomiphene citrate as a first line treatment option remains unanswered and a clear answer would have important clinical implications for infertility specialists.[10]

This study was conducted to see the efficacy of letrozole and clomiphene citrate in achieving pregnancy in patients with anovulatory infertility.

## MATERIAL AND METHODS

This randomized controlled trial was conducted from January 2012 to June 2014. Total 212 females of 20-38 years with anovulatory infertility (patients having contraceptive free sexual intercourse for more than one year and not getting pregnancy despite having normal pelvic ultrasonography, bilateral normal tubal patency on hysterosalpingography and normal male factor), presented to the OPD of Obstetrics & Gynaecology, Bahawal Victoria Hospital, Bahawalpur, were selected. Patients with other causes of infertility i.e. tubal factors, male factor and unexplained infertility, Histroy of previous surgery related to genital tract and histroy of drugs likely to interfere with ovulation were excluded. After approval from local ethical committee, all patients had given informed consent for participation in the study. Patients included in the study were divided into two groups by lottery method. Detailed history about menarche age, menstrual cycles and duration of infertility was taken from each patient.

All cases in Group A were treated with clomiphene citrate orally once a day for 5 days (3-7) of menstrual cycle for up to 5 menstrual cycles. Occurrence of pregnancy was awaited for 5 menstrual cycles after start of therapy. While in Group B, all patients were treated with 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 called in outpatient department 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 (levels of ≥5 mIU/ml of β-HCG was taken as occurrence of pregnancy and level <5 mIU/ml was taken as absent pregnancy). Final outcome was measured in terms that patient had reported back to researcher in OPD at monthly basis up to five menstrual cycles. All the data was entered and analyzed by using SPSS version 14.0. Age and duration since marriage in both groups were presented by mean ± SD. Outcome variables like efficacy in terms of achieving pregnancy in both groups was presented by frequency and percentages. Efficacy of both treatment regimens was compared in two groups by chi square test. P value ≤0.05 was considered as statistically significant.

## RESULTS

The mean age of women in group A was 26.67±4.23 years and in group B was 26.24±4.18 years with majority of the patients 136 (64.15%) were between 21 to 30 years of age as shown in Table I. The mean duration since marriage in group A was 4.06 ± 1.95 years and in group B was 4.26±2.12 years with majority of the patients 151 (71.23%) had <5 years of duration since marriage. Efficacy of Group A (clomiphene citrate group) was 11 (10.38%) while in Group B (letrozole group) was 23 (21.70%) as shown in Table II (p=0.02).

## DISCUSSION

The medical management of anovulation is complex because it entails initiating a multitiered approach to patient care. First and foremost, the clinician should be well acquainted with the most common etiologies and able to rule them out,

**Table 1: Age distribution of study patients with anovulator infertility.**

| Age (years) | Group A (Clomiphene Group) (n=106) | | Group B (letrozole) (n=106) | | Total (n=212) | |
|---|---|---|---|---|---|---|
| | No. of patients | Percentage | No. of patients | Percentage | No. of patients | Percentage |
| 20-30 | 67 | 63.21 | 69 | 65.09 | 136 | 64.15 |
| 31-38 | 39 | 36.79 | 37 | 35.91 | 76 | 35.85 |
| Mean±SD | 26.67±4.23 | | 26.24±4.18 | | 26.56±4.17 | |

**Table 2: Percentage of patients according to efficacy between study groups.**

| | | Group A (Clomiphene Group) (n=106) | | Group B (letrozole) (n=106) | |
|---|---|---|---|---|---|
| | | Number of Patients | Percentage | Number of Patients | Percentage |
| Efficacy | Yes | 11 | 10.38 | 23 | 21.70 |
| | No | 95 | 89.62 | 83 | 78.30 |

specifically those that can pose serious dangers to a patient's immediate health. Luckily, anovulation usually manifests in a clinical setting geared toward the treatment of chronic diseases and conditions, which provides the precision necessary for an accurate diagnosis.[11]

The mean age of patients in this study was 26.56 ± 4.17 years with majority of the patients 64.15% were between 21 to 30 years of age in both groups. These results were very much comparable to studies of Fouda UM et al[12] and Sherif F et al[13] who had shown a mean age of 26 years and 27 years respectively. On the other hand, Hussain NHN et al[14] in his study has shown a larger mean age i.e. 29 years, compared to our study. Mean duration since marriage was 4.27 ± 2.09 years in this study which is very much comparable to the study of Hussain NHN et al[14] who had observed this as 4.5 years, but a little higher than Fouda UM et al[12] who had found this as 3.6 years. This late presentation in our society may be due to Quack culture, lack of awareness, some social constraints and economic hurdles.

The data obtained from the present study revealed that orally administered letrozole and clomiphene citrate are both effective in the treatment of anovulatory infertility and that letrozole is more effective and more safe than clomiphene citrate. Efficacy of letrozole was 21.7% while clomiphene citrate group was 10.38% with p-value of 0.02 as observed in this study. Polyzos et al[15] and Requena et al[16] in their studies of comparing clomiphene citrate with letrozole for superovulation in patients with unexplained infertility undergoing IUI revealed that although letrozole induced fewer mature follicles compared with clomiphene citrate the pregnancy rate was comparable between both management options. In contrast, a clinical trial comparing the efficacy of letrozole and clomiphene for ovulation induction in 107 infertile patients with PCOS showed no significant difference in the number and size of mature follicles, but a higher pregnancy rate in the letrozole group was observed.[17]

Atay V et al[18] in his randomized study has compared the two regime i.e. letrozole versus clomiphene citrate in treating anovulatory infertility and found the letrozole superior as compared to clomiphene citrate. He has found the ovulation rate (82.4% Vs 63.6%, p=0.01) and the clinical pregnancy rate (21.6% vs. 9.1%, p=0.03) were significantly higher in the letrozole group as compared to the clomiphene group. On the other hand, there are many previous studies which have shown no statistically significant difference between clomiphene citrate and letrozole in ovulation rate. In a study by Kar et al[19], ovulation rate was 60.78% with clomiphene citrate and 73.08% with letrozole, which was not statistically significant (p=0.39).

In the largest RCT trial involving 438 women wit1h PCOS done by Badawy et al[20] concluded that no benefit was observed with the use of letrozole as first line therapy, especially since the cost of the drug is comparatively high. But he has found that endometrial thickness in the women who received clomiphene was significantly higher than in the Letrozole group which is contrary to the traditionally accepted view. In another randomized controlled trial (RCT) by Bayar et al[21] has also shown no significant difference in either the ovulation rate or the clinical pregnancy rate between the two groups.

In his study Roy et al[22] 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 al[14], pregnancy rate found was notably higher in the Letrozole group compared to the Clomiphene citrate group with 25.3% and 16.0% respectively; however, this was not statistically significantly. The pregnancy rate observed in our study was also consistent with other reported studies such as that by Mitwally et al.[23] Letrozole has now been in use as an ovulation induction agent for more than a decade. Even though emerging evidence suggests that it is an effective ovulation induction agent, comparable if not better than clomiphene.[10]

## CONCLUSION

This study concludes that orally administered letrozole is more effective in achieving pregnancy than clomiphene citrate in the treatment of anovulatory infertility.

We recommend that letrozole should be used as a first line therapy in anovulatory infertile women.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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