

Comparison of Letrozole versus Clomiphene Citrate on Ovulation and Achieving a Successful Pregnancy

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ABSTRACT

Am: To compare the effectiveness (in terms of achieving pregnancy) of letrozole vs clomiphene citrate in anovulatory infertile women.

Methods: This randomized controlled trial study was carried out at the Department of Obstetrics & Gynecology, Allama Iqbal Memorial Teaching Hospital, Sialkot from March 2016 to September 2016. A total of 224 patients, 18 to 40 years of age with anovulatory infertility were included. Patients with H/o previous surgery, hypothyroidism and hyperprolactinemia were excluded. Then selected patients were placed randomly into two groups i.e., Group A (clomiphene citrate) & Group B (letrozole), by using lottery method. Outcome variable like effectiveness was noted.

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 anovulatory infertility as compared to the clomiphene citrate.

Keywords: Anovulatory 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 ovaries.¹ 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. 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 flushes⁶.

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 anovulatory infertility so that some practical recommendations could be made to achieve maximum number of pregnancies in anovulatory infertile women with more efficacious treatment regime.

SUBJECTS AND METHODS

This randomized controlled trial study was carried out at the Department of Obstetrics & Gynecology, Allama Iqbal Memorial Teaching Hospital, Sialkot from March 2016 to September 2016. All females with anovulatory infertility (as-per-operational definition), age (18-40) years were included. Females with history of pelvic surgery (assessed on history

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and medical record), hypothyroidism (assessed on history and medical record), hyperprolactinemia (assessed on history and medical record) and known to be allergic to these drugs were excluded. Anovulatory 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. A total of 224 patients with anovulatory infertility (as per-operational definition) presenting to OPD fulfilling the inclusion/exclusion criteria were selected. 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.

The collected information was analyzed by computer software SPSS 20. 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 9 (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

Groups	Efficacy		P value
	Yes	No	
A	19 (16.6%)	3 (83.04%)	0.05
B	37 (33.04%)	75 (66.6%)	

DISCUSSION

The purpose of the study was to compare the effectiveness (in terms of achieving pregnancy) of letrozole vs clomiphene citrate in anovulatory 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 Ibrahim⁸ 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 et al¹⁰ reported that pregnancy rate was significantly higher in the letrozole group as compared to the clomiphene group. Bayar 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

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	10 (13.7%)	63 (86.3%)	24 (32%)	51 (68%)	0.008
31 - 40	9 (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 (years)	Group A (n = 112)		Group B (n=112)		P value
	Effectiveness		Effectiveness		
	Yes	No	Yes	No	
< 5	12 (16.9%)	59 (83.1%)	26 (37.68%)	43 (62.32%)	0.006
> 5	7 (17.07%)	34 (82.3%)	11 (25.58%)	32 (74.42%)	0.342

CONCLUSION

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

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