

Research Article

Comparative study between letrozole and clomiphene citrate for achieving a successful pregnancy in anovulatory infertile women

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ABSTRACT

Objectives: Comparative study between letrozole and clomiphene citrate for achieving a successful pregnancy in anovulatory infertile women

Material and methods:

This comparative study was conducted at Department of Obstetrics & Gynecology Sheikh Zaid Hospital, Rahim Yar Khan from January 2017 to June 2017. 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 ovaries². 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%.⁴ Any

condition whether primary or secondary, that results in either a persistent elevation or an insufficient attainment of estrogen levels can inhibit ovulation through a disruption of the mechanisms that induce LH surge. To achieve the corresponding changes within the cycle, estradiol levels must rise and fall appropriately.⁴

The HPO axis is the target of first line ovulation-induction therapy^{3,7,5,10} 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.^{3,7,9} But, the oral fertility drugs are the most commonly used therapy for ovarian dysfunction worldwide.

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.⁸ 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.^{5,8}

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.^{8,10}

Various studies^{4,5} have shown a significant difference between rate of ovulation and pregnancy and a higher miscarriage rate in patients undergoing Clomiphene therapy. Some prospective pilot studies have been performed and the results showed that letrozole cycles have a significantly higher pregnancy rate than Clomiphene.^{2,3} The study by Ibrahim MI¹ showed pregnancy rate of 23.07% in the letrozole group and 10.68% in the clomiphene group.

Literature confirms that letrozole has a definitive role in anovulatory women who have not responded to the clomiphene therapy.^{4,5,8,9} However its role as an alternative to clomiphene as first line therapy continues to be debated.^{7,10}

Therefore, there was a need for more study to find out the better treatment for ovulation induction and achieving a successful pregnancy that may be offered to the patients in future. 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.

OPERATIONAL DEFINITIONS:

- **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.

MATERIAL AND METHODS

This comparative study was conducted at Department of Obstetrics & Gynecology Sheih Zaid Hospital, Rahim Yar Khan from January 2017 to June 2017.

Inclusion Criteria:

- All females with anovulatory infertility (as-per-operational definition).
- Age (18-40) years.
- Informed consent taken to participate in the study

b. Exclusion Criteria:

- History of pelvic surgery (assessed on history and medical record).
- Hypothyroidism (assessed on history and medical record).

- Hyperprolactinemia (assessed on history and medical record).
- Known to be allergic to these drugs.

DATA COLLECTION PROCEDURE:

After approval from ethical review committee a total of 224 patients with anovulatory infertility (as per-operational definition) presenting to OPD in Sheih Zaid Hospital, Rahim Yar Khan fulfilling the inclusion/exclusion criteria was selected. After a patient taken informed consent for participation in study all selected cases were offered to pick up a slip from total mixed up slips (half-slips contained letter A and half contained letter B) and she was placed in the respective group. 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 (Annexure-1)

STATISTICAL ANALYSIS:

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.

Table-I: Age distribution for both groups (n=224).

Age (years)	Group A (n=112)		Group B (n=112)		Total (n=224)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-30	73	65.18	75	66.96	148	66.07
31-40	39	34.82	37	33.04	76	35.97
Mean \pm SD	26.72 \pm 6.02		26.87 \pm 6.33		26.76 \pm 6.19	

Table-II: Distribution of patients according to duration of infertility in both groups.

Duration of infertility	Group A (n=112)		Group B (n=112)		Total (n=224)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
< 5 years	71	63.39	69	61.61	140	62.50
>5 years	41	36.61	43	38.39	84	37.50
Mean \pm SD	3.23 \pm 2.19		3.68 \pm 2.34		3.47 \pm 2.21	

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, obesity (i.e. BMI>30) were controlled through stratifications and post stratification chi Square was applied to see the effect of these on effectiveness. P value \leq 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. Majority of the patients 148 (66.07%) were between 18 to 30 years of age as shown in Table I.

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. Majority of the patients 140 (62.50%) had < 5 years of duration of infertility as shown in Table II. Frequency of patients according to obesity in both groups is shown in Figure IV.

Effectiveness of Group A (clomiphene citrate group) was 19 (16.96%) while in Group B (letrozole group) was 37 (33.04%) as shown in Table III (p-value = 0.005). Comparison between effectiveness of both groups according to age groups is shown in Table IV. Table V & VI have shown comparison between effectiveness of both groups according to duration of infertility and obesity respectively.

Figure IV: Frequency of patients according to obesity in both groups.

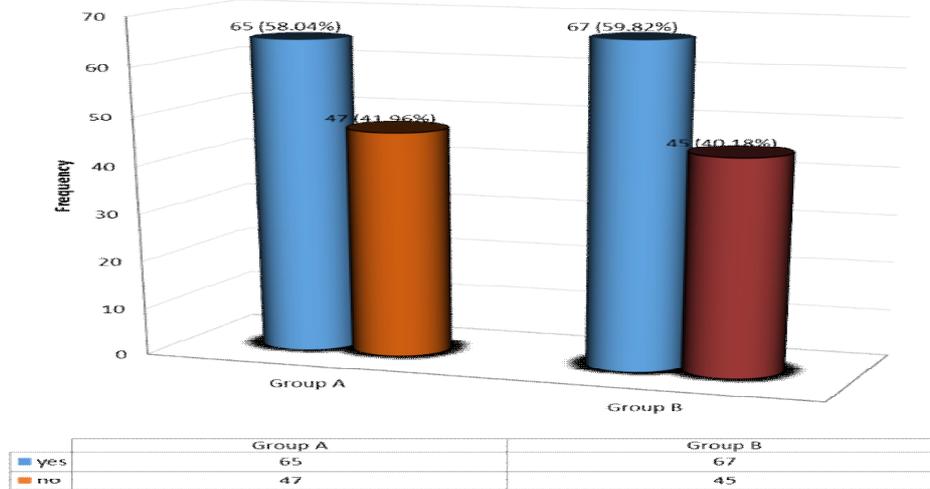


Table III: Distribution of patients according to effectiveness between both Groups.

		Group A (n=112)		Group B (n=112)	
		No. of Patients	%age	No. of Patients	%age
EFFECTIVENESS	Yes	19	16.96	37	33.04
	No	93	83.04	75	66.96

➤ **P value is 0.005 which is statistically significant.**

Table IV: 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 V: 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

Table VI: Comparison between effectiveness of both groups according to obesity

Obesity	Group A (n=112)		Group B (n=112)		P-value
	effectiveness		effectiveness		
	yes	no	yes	no	
Yes	11 (16.92%)	54 (83.08%)	21 (31.34%)	46 (68.66%)	0.053
No	08 (17.02%)	39 (82.98%)	16 (35.56%)	29 (64.44%)	0.043

DISCUSSION

The most common cause of infertility in women is anovulation. There are many drugs used for induction ovulation among isolated unovulation non-polycystic ovarian syndrome (PCOS). The

first line oral treatment is non-steroidal selective estrogen receptor modulators (SERM).¹¹ Clomiphene citrate has been introduced in 1956.¹² That is the first-line method of ovulation induction in women with anovulatory infertility. Since 1962 it has been the drug of choice for oral

ovulation induction over the last 50 years.¹³ Clomiphene can induce ovulation in 80% of anovulatory women but only 40% of women became pregnant.¹⁴ Pregnancy rate per cycle can be 10-20% (2) and as high as 60% after six cycles and 97% after 10 cycles.¹⁵ Unfortunately, 20-25% of the women are resistant to clomiphene citrate and fail to ovulate.¹⁶ Letrozole increases FSH levels and therefore increases in the number of multiple mature follicles¹⁷ and do not have adverse endometrial effects because that half life is shorter than clomiphene, so increased pregnancy rate.¹² In most studies, letrozole used for induction ovulation in polycystic ovarian disease (PCOS), but data in non PCOS patients is limited. I have conducted this study 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 Ibrahim MI¹ showed pregnancy rate of 23.07% in the letrozole group and 10.68% in the clomiphene group.

In a study¹⁸ on 150 anovulatory infertile women who had isolated non- polycystic ovarian syndrome (PCOS), randomized to 3 groups. Group A received clomiphene 50 mg to maximum 150 mg for 5 days, Group B received tamoxifen 10mg to maximum 30 mg for 5 days, Group C received letrozole 2.5 mg for 5 days, to maximum 7.5 mg until ovulation was induced. If ovulation failed to occur with 5 days treatments, drug continued for 7 days. Overall ovulation rate was 60 (73.4%), this rate in group A was 39 (78%), in group B it was 24 (68%) and in group C was 37 (74%). Pregnancy rate in groups A, B and C were, 32 (64%), 20 (40%), and 25 (50%) respectively, and live birth rate was 22 (44%) in A, 17 (34%) in

B and 21 (42%) in C. Miscarriage rate with clomiphene was 10 (20%) while this was 3 (6%) in tamoxifen and 4 (8%) in letrozole group (p=0.05).¹⁸

Mitwally and Casper,¹⁹ in another study, evaluated the use of Letrozole with exogenous FSH in 12 patients with unexplained infertility and a history of poor ovarian response to FSH in at least two previous cycles. Previous poor responders were defined as those who had less than three follicles ≥ 18 mm in diameter on the day of HCG administration.²⁰ Letrozole was administered from days 2–6 at a dose of 5 mg/day and gonadotrophin treatment (75 IU/day) was started on days 7–9. Intrauterine insemination was performed in all cycles. Improved response to exogenous gonadotrophic stimulation with Letrozole co-treatment was noted by the lower gonadotrophic dose and it was associated with higher number of mature follicles. Three (21%) pregnancies were achieved. Healey et al. reported similar findings in 205 IUI cycles; addition of Letrozole to FSH treatment decreased FSH requirement and increased the number of preovulatory follicles.²¹

Atay V et al randomized 106 women with PCOS (55/51) to receive either letrozole (2.5 mgs) or clomiphene citrate (100 mgs/day).²² 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 with the authors recommending letrozole as a better first line approach. In another randomized controlled trial (RCT) Bayar U et al compared letrozole versus clomiphene citrate as a first line ovulation inducing agents.²³ There was no significant difference in either the ovulation rate or the clinical pregnancy rate between the two groups [(65.7% vs 74.7%) and (9.1% vs 7.4%)].

Begum et al²⁴ studied a different category of women, recruiting for their RCT women who did not respond to 100 mg of clomiphene. The study group received 7.5 mgs of letrozole while the control group was given clomiphene citrate at a dose of 150 mg. Not unexpectedly, the ovulation

rates in the letrozole arm were significantly higher as compared to the clomiphene arm (62.5% vs 37.5%). In a study by Karet al⁸, 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 al⁴ 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 al²⁵, 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 significant. In a local randomized controlled trial, the mean age of women in clomiphene group was 26.67 ± 4.23 and in letrozole group was 26.24 ± 4.18 years. The mean duration since marriage in clomiphene group was 4.06 ± 1.95 years and in letrozole group 4.26 ± 2.12 years. Efficacy of clomiphene citrate was 10.38% while that of letrozole was 21.70% ($p=0.02$).²⁵

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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