

## Comparison of Letrozole and Clomiphene Citrate Efficacy along with Gonadotrophins in Controlled Ovarian Hyperstimulation for Intrauterine Insemination Cycles

Fauzia HaqNawaz<sup>1\*</sup>, Saadia Virk<sup>2</sup>, Tasleem Qadir<sup>3</sup>, Saadia Imam<sup>3</sup>, Javed Rizvi<sup>2</sup>

1- MRCOG (UK), FCPS (Pak); LMCC (Canada) Aga Khan University Hospital, Karachi, Pakistan

2- FRCOG Australian Concept Fertility Centre, Karachi, Pakistan

3- FCPS Australian Concept Fertility Centre, Karachi, Pakistan

### Abstract

**Background:** We performed this study to investigate and compare the effects of Letrozole and gonadotrophins versus Clomiphene Citrate and gonadotrophins in women undergoing superovulation for Intrauterine Insemination (IUI).

**Methods:** We performed this prospective cohort study at Australian Concept and Fertility centre, Karachi Pakistan. Women younger than 40 years of age with patent fallopian tubes and infertility of more than 2 years in duration who were undergoing IUI and gonadotrophins therapy were divided into two groups, one received Letrozole for 5 days and another received Clomiphene Citrate for 5 days.

**Results:** All 500 IUI treatment cycles conducted from March 2008 to March 2010 were included. Patients co-treated with Letrozole required fewer gonadotrophins administrations (median difference, 300 IU (95% confidence interval (CI), 225–375 IU), developed more follicles larger than 14 mm (median difference, 1 follicle, 95% CI, 1–2 follicles), and had a thicker endometrium (median difference, 1 mm, 95% CI, 0.4–1.6 mm). The pregnancy rate was not significantly different between two groups (11% vs. 12.6%).

**Conclusion:** The addition of Letrozole to gonadotrophins decreases gonadotrophins requirements and improves endometrial thickness, without a significant effect on pregnancy rates. An improved pregnancy rate has been observed in older age group, >35 years with Letrozole.

**Keywords:** Gonadotrophin, Infertility, Intrauterine insemination, Letrozole, Pregnancy.

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\*Corresponding Author:  
FH Fauzia HaqNawaz,  
MRCOG Aga Khan University Hospital, Karachi, Pakistan  
E-mail:  
fauzia.nawaz@gmail.com

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### Introduction

Controlled ovarian hyperstimulation (COH) with IUI is often used for treatment of unexplained infertility, anovulation, early stage endometriosis and borderline male factor infertility. Clomiphene Citrate (CC), requiring minimal monitoring, is often used for this purpose (1, 2). Anovulation is responsible for about 20% of female infertility of which polycystic ovary syndrome (PCOS) is a leading cause. In euestrogenic anovulation, Clomiphene Citrate (CC) remains the

primary therapy to induce ovulation. Clomiphene Citrate is an antiestrogen that leads to a 60%–85% ovulation rate and a 10%–20% pregnancy rate (PR) per cycle. This disparity in outcome is related to the antiestrogen effect of CC, which involves long lasting estrogen receptor (ER) depletion.

Letrozole is an oral, potent, reversible, and highly selective Aromatase inhibitor that prevents an drogen-to-estrogen (E) conversion. It has been

recently proposed as an alternative to CC and a first-line treatment agent to induce ovulation in anovulatory and ovulatory infertile patients.

The aim of this study was to compare the effectiveness of Letrozole and CC for ovulation induction in patients with unexplained infertility, early stage endometriosis, PCO's and borderline male factor infertility. Therefore the aim of this study was comparison of efficacy of Letrozole and Clomiphene Citrate along with gonadotrophins in controlled ovarian hyperstimulation for intrauterine insemination cycles.

### Methods

This prospective Cohort study was performed at Australian Concept and Fertility Centre Karachi Pakistan. Five hundred consecutive women with unexplained infertility, PCOS early stage endometriosis, and borderline male factor infertility were recruited for study from March 2008-March 2010. The women were evaluated and counseled by the consultants for IUI treatment either with Clomiphene Citrate (clomid), (OBS Pharma, Pakistan) and gonadotrophins (HMG, Massone Pharma, Argentina) or Letrozole (Novartis Pharma, Australia) and HMG. From treatment and analysis point of view, two groups were formulated, group A received Letrozole (5 mg) for five days and gonadotrophins (HMG) 75 IU once daily for 3–5 days, while group B received Clomiphene Citrate (50 mg) for 5 days and gonadotrophins (HMG) in a dose of 75 IU for 3–5 days based on follicular response on ultrasound at day 8 of the cycle. The patients were assigned to either group A or B by random sampling technique. Inclusion criteria included infertility lasting more than 2 years, normal hormonal profile FSH, LH, Prolactin & Testosterone. Tubal patency documentation by normal hysterosalpingography and/or diagnostic laparoscopy was noted and confirmed. Patients with stage I or II endometriosis and normal semen analysis were categorized as early stage endometriosis patients. Clinical, biochemical, ultrasonic and metabolic features of women with infertility were recorded on a data collection form with respect to age, type and duration of infertility, previous miscarriages and live births. The criteria for borderline male factor infertility were as follows: sperm concentration <10 million/ml and motility of <20% (4). Swim up preparation should show live count of 8 million/ml and rapid linear progression of 50%.

Out of 500 patients, two groups were formulated, group A received Letrozole (n=300) and group B received CC (n=200). Patients were monitored with Transvaginal Ultrasonography. Human chorionic gonadotrophin (Pregnyl), (Organon, Netherland) at a dose of 10,000 IU was used to trigger ovulation when at least one follicle exceeding 18 mm in diameter and an endometrial thickness of >7 mm was noted.

Intrauterine insemination was performed in women with borderline male factor infertility, early endometriosis, PCOS and unexplained infertility both in the Letrozole (N: 300) and CC (N: 200) groups. In our study, single IUI was performed 36 hr after administration of HCG. Ovulation was assumed to have occurred during this time period.

The statistical analyses were performed using SPSS, version 17. The data were expressed as median (range). Mann-Whitney U tests were used to compare nonparametric data. Categorical variables were compared by using Chi square test, for continuous variables we used a t-test. To compare the outcome in two groups, we used two tailed test of significance and p-value was considered significant if <0.05.

### Results

Five hundred women with sub fertility were recruited for this study, three hundred women in group A and two hundred women in group B. Demographic features are shown in table 1. It has been clear that except for age, the rest of features like BMI, duration of subfertility, day 2 FSH, LH, and prolactin levels are comparable. The median age in group A was relatively higher i.e. 35 years vs. 31 years (p=0.01) (Table 1). In both groups there was almost equal proportion of different causes of subfertility like PCOS, early endometriosis and borderline male factor sub fertility.

No patient had a lack of follow-up in this study. Women were scheduled for IUI in both groups after 36 hr of ovulation triggered with HCG.

The ovulation induction data of the two groups are given in table 2. The median number of follicles >18 mm in diameter and endometrial thickness of 7 mm on the day of HCG administration were comparable among the two groups; however, the trigger occurred one day earlier than CC group. In the CC group, the bilayer endometrial thicknesses on the day of HCG administration were >8 mm; none of the women achieved pregnancy on endometrial thickness <7 mm in both

**Table 1.** Demographic features of Letrozole and CC-treated groups

Variable	Letrozole + HMG Group A	CC+ HMG Group B	P-value
No. of patients	200	300	
Female age (years)	35 (33–44)	31 (24–39)	0.01
Duration of infertility (years)	4 (1–9)	4 (3–8)	0.76
Day-2 FSH (mIU/ml)	7 (3–12)	6 (3–11)	0.11
Day-2 LH (mIU/ml)	6(4–15)	7 (3–17)	0.06
Serum Prolactin (mg/dl)	11.2(8–25.2)	10.4(7–24.7)	0.99
BMI kg/m <sup>2</sup>	24.1(18.2–32)	22.4(18.6–31.1)	0.43

groups. There was a significant positive correlation between endometrial thickness and follicular growth and pregnancy outcome.

Ovulation occurred in 81% and 85% of the cycles in Letrozole and CC groups, respectively (p=0.71). Twenty six women (11%) and 35 (12%) women conceived in the Letrozole and CC groups, respectively (p=0.09) (Table 2). Rates of miscarriage and live birth were also comparable in both groups. The risk of multifetal pregnancy was 2% in both groups whereas no untoward side effects were noted in the Letrozole and the CC groups.

### Discussion

There have been multiple studies that have compared the results of Letrozole and Clomiphene citrate with varying usage of each and with diverse results (8, 10).

We included 500 infertile couples, who were suitable candidates for superovulation and IUI; however, the characteristics of patients in the two groups were not different in terms of female age, BMI, duration of infertility and profile for infertility factors.

There is a paucity of data on the use of Letrozole

as an ovulation induction agent in anovulatory infertility and as a part of empirical treatment (6–8). Mitwally and Casper (3) have reported the use of Letrozole in 12 patients with polycystic ovary syndrome (PCOS) and 10 patients with unovulatory infertility. Letrozole was given in a dose of 2.5 mg on days 3–7 of menses. In the PCOS group, ovulation occurred in nine patients (75%) and pregnancy was achieved in three (25%). In un-ovulatory patients, ovulation occurred in all cycles. The mean number of follicles measuring >15 mm in diameter on the day of hCG administration was 2.3 (range, 1–4). One pregnancy (10%) was reported.

Mitwally and Casper (9), 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 (10). 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 gona-

**Table 2.** Ovulation induction and pregnancy outcome of letrozole and CC groups

Variable	Letrozole+ HMG	CC+HMG	P-value
No. of follicles >18 mm in diameter on the day of hCG	2.5 (0–5)	1.8 (0–4)	0.06
Endometrial thickness the day of hCG (mm)	9 (5–12)	8 (4–10)	0.67
OHSS	0	0	
Multiple pregnancy (twins)	2/200	6/300	0.56
Miscarriages	4/200	7/300	0.32
Pregnancy rate (%)	26/200(11%)	35/300 (12%)	0.9
Live births rate	22/26 (84.6%)	28/35(80%)	0.32

dotrophic 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 (6). Although endometrial thickness was decreased, no negative effect on pregnancy rates (PR) was noted.

In women with diminished ovarian reserve, there is a poor response to ovulation induction medications. In some, it is due to the lack of oocytes; in others, however, it is due to a decrease in follicular FSH receptors. With the use of Letrozole, an increase of androgen is known to increase these receptors. Thus in theory, Letrozole could be a unique and valuable treatment for a subset of women with diminished ovarian reserve.

One of the findings in our study was that better ovulation and pregnancy rates in women with > 35 years are achieved with the use of Letrozole and it revealed less need for gonadotrophins. Our study findings correlate well with the findings of Mitwally et al. (3) who studied women with poor response to gonadotropins in previous stimulation cycles (less than three dominant follicles). They were subsequently given Letrozole at 2.5 mg on days 3–7, followed by gonadotropins at 50–250 IU until lead follicles were measured to be more than 18 mm. The subjects then underwent intrauterine insemination. In the previous cycles, the total number of mature follicles was 1.9; with Letrozole and gonadotropins, 3.3 mature follicles were developed. The pregnancy rate was 21% in these patients (3).

In this study, we compared Letrozole with CC as the first-line therapy for ovulation induction in patients with borderline male factor infertility, early-stage endometriosis, and unexplained infertility. Being not a blinded study and quasi-randomization are weaknesses of our study. Because our study was a pilot study and the sample size was limited, the duration of infertility was significantly higher in Letrozole group. Despite this difference, PRs of the two groups were comparable. All ovulation induction outcome measures, per follicle >15 mm in diameter, were comparable among the CC and Letrozole groups. Pregnancy rates were also comparable.

Although median endometrial thickness was comparable among CC and Letrozole groups, in

none of the Letrozole cycles it was less than 5 mm. This lack of detrimental effect on endometrial thickness may be a favorable finding with Letrozole treatment. There are limited data on the effect of Letrozole on endometrium. Cortinez et al. (7), in Letrozole-treated patients, reported normal morphology of endometrium. Mitwally and Casper (3) reported significantly higher endometrial thickness on the day of HCG administration in Letrozole compared with CC, despite significantly lower E2 levels in the former. However, no significant difference was noted in other studies (7, 10).

### Conclusion

In summary, the results of this study suggest that the aromatase inhibitor, Letrozole, can be used as an alternative first-line treatment for ovulation induction in selected groups of infertile patients, and may reduce the need for gonadotrophins in patients undergoing superovulation with IUI.

### Conflict of Interest

Authors declare no conflict of interest

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