

Comparison of the Efficacy of Letrozole and Clomiphene Citrate for Ovulation Induction in Infertile Women with Polycystic Ovary Syndrome

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ABSTRACT

Aim: To compare the efficacy of letrozole with clomiphene citrate for ovulation induction in infertile patients with polycystic ovarian syndrome (PCOS).

Methods: This clinical trial study was carried out at Gynae unit 2 Lady Willingdon Hospital Lahore from 1st July 2012- 30th June 2013. Total 100 patients of PCO were included in the study. Diagnosis of PCO was made on Rotterdam criteria. In this clinical trial, 100 infertile patients with PCOS received either 100 mg clomiphene citrate (n=50) or 2.5mg letrozole (n=50) daily since day 2-6 of their menstrual cycle. Human chorionic gonadotropin (hCG) was administered at a dose of 10,000IU when at least 1 mature follicle (17-25mm) was detected. Timed intercourse was advised to the patients after 24-36 hrs of HCG injection. Then the number of follicles, endometrial thickness, P₄ on day 21, ovulation rate, and pregnancy rate were measured in both groups.

Results: Monofollicular development was statistically significantly, greater in the Let group (CC 55.76%, Let 78.32%). There was no statistically significant difference between the two groups in endometrial thickness on the day of HCG injection (CC 7.62±1.95mm, Let 7.65±1.98mm P=0.91). Similarly, there was no statistically significant difference between the two groups in days to ovulation, and serum P₄ on D₂₁. The ovulation rate was 60.02% in CC group and 72.28% in Let group. The pregnancy rate was in 7.42% CC group and 20.55% in Let group. There was one multiple pregnancy in cc group.

Conclusion: Letrozole might be an acceptable alternative to clomiphene citrate to induce ovulation and pregnancy in PCOS patients.

Keywords: Letrozole, clomiphene citrate, PCOS, infertility.

INTRODUCTION

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%. Polycystic ovary syndrome is a common disease that is closely related to ovulation dysfunction and 7% of women of childbearing age are afflicted with it¹. 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 a male factor problem². Ovulation induction is a way to treat infertility in PCOS which is possible through medication or surgery¹. Clomiphene citrate (CC) is the most commonly used oral agent for the induction of ovulation. It is a nonsteroidal selective estrogen receptor modulator that has predominant antiestrogenic action resulting in long-lasting estrogen receptor depletion. Side effects include antiestrogenic effects systemically and on the

endometrium and cervical mucus³. Clomiphene citrate is considered as the drug of choice for first line treatment of anovulatory dysfunction for a variety of reasons. It is orally administered, has few side effects, is easily available and is inexpensive. Although ovulation rates are in the range of 70-80% the actual pregnancy rates are significantly lower at around 30-40%^{4,5}. Clomiphene resistance together with side effects like multi-follicular development and cyst formation are areas of concern, the desire for an effective alternative persists².

Letrozole is a potent, nonsteroidal, aromatase inhibitor, originally used for postmenopausal breast cancer therapy, at present its only registered indication³. It was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance^{6,7}. Letrozole has found acceptance in various clinical situations and the indications for use have expanded^{8,9}. 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

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estrogen receptor blockage. Letrozole is also cleared from the circulation more rapidly due to a shorter half life (48 hours) as compared to clomiphene citrate which may take up to 2 months due to its prolonged half life (2 weeks)². This study was conducted to compare the effects of Letrozole and Clomiphene citrate for ovulation induction in women with PCOS.

MATERIAL & METHODS

This clinical trial study was carried out at Gynae unit 2 Lady Willingdon Hospital Lahore from 1st July 2012-30th June 2013. Total 100 patients of PCO were included in the study. Diagnosis of PCO was made on Rotterdam criteria. Patients with hyperprolactinemia, thyroid disorder, male factor infertility, suspected tubal factor, endometriosis and unexplained infertility were not included in the study. The subjects were randomly divided into two groups including 50 patients in each group. Patients of group A were given clomiphene citrate 100mg and patients of group B were given letrozole 2.5mg daily for 5 days starting on day 2 of menstrual cycle. Follicular monitoring was done by transvaginal sonography starting on day 8 of menstrual cycle till a follicle attained 18-25mm diameter. A single injection of HCG 10,000 IU was given IM if at least one follicle attained 17-18 mm. Timed intercourse was advised to the patient after 24-36 hrs of HCG injection. A final scan after 48 hrs was done for all patients to confirm rupture of follicle. If not ruptured, a repeat scan was done after 72 hrs to diagnose luteinized unruptured follicle. Ovulation was confirmed by sonographic finding and day 21 serum progesterone. Serum P₄ on day 21 was done for all patients. Luteal support (Tab duphastone 10mg orally daily) was given to all patients. Serum beta human chorionic gonadotropin (βHCG) was done after one week of missed periods to confirm the pregnancy. Ongoing pregnancy diagnosed following visualization of cardiac activity by TVS. Women who failed to ovulate with 100 mg clomiphene citrate or 2.5mg letrozole were dropped from the study. Primary outcome measures are ovulation rate, endometrial thickness, mono Vs. multifollicular rate, and days to ovulation. Secondary outcome measures were pregnancy and miscarriage rate. Chi-square and student's 't' test were carried out for statistical analysis.

RESULTS

Total 100 PCO patients with infertility were included in the study. There were 50 patients in the CC group and 50 patients in the letrozole group. Age, duration of infertility, BMI, presenting signs and symptoms were similar in both groups (Table 1). Monofollicular

development was statistically significantly, greater in the Let group (CC 55.76%, Let 78.32%). There was no statistically significant difference between the two groups in endometrial thickness on the day of HCG injection (CC 7.62±1.95 mm, Let 7.65±1.98 mm $P=0.91$). Similarly, there was no statistically significant difference between the two groups in days to ovulation, and serum P₄ on D₂₁ (Table 2). The ovulation rate was 60.02% in CC group and 72.28% in Let group. The pregnancy rate was in 7.42% CC group and 20.55% in Let group. There was one multiple pregnancy in cc group (Table 3).

Table 1 Patient characteristics of both CC and Let groups

	Group A	Group B
Age (years)	24.26±2.33	24.29±2.31
BMI (kg/m ²)	25.89±3.31	25.91±3.32
Duration of infertility (years)	3.12± 2.02	3.18±2.12

Table 2: Outcome of ovarian stimulation

	Group A	Group B
Monofollicular development %	55.76	78.32
Multifollicular development %	44.24	21.68
Endometrial thickness (mm)	7.62±1.95	7.65±1.98
Days to ovulation	14.1±3.31	13.13±2.98
P ₄ on Day 21(ng/ml)S	10.56 ±6.45	11.64 ±6.52

Table 3: Outcome of treatment

	Group A	Group B
Ovulation rate (%)	60.02	72.28
Pregnancy rate (%)	7.42	20.55
Multiple pregnancy (%)	01	None

DISCUSSION

Clomiphene citrate has been used for ovulation induction since 1960s. It is still considered first-line drug for anovulatory PCOS women. However, clomiphene resistance (15-20%), endometrial thinning, and poor cervical mucus (15-50% of cases) makes it ineffective in many situations^{10,11,12,13,14}. Letrozole, which is an aromatase inhibitor, has been explored as a good alternative by many researchers, but the evidence about its efficacy as compared to clomiphene is conflicting.

Clomiphene, a non steroidal compound, structurally similar to estrogen, blocks estrogenic hypothalamic receptors, resulting in blinding of the hypothalamus-pituitary axis to endogenous circulating estrogen. This in turn triggers release of FSH from the anterior pituitary following alterations in GnRH pulsatility. Clomiphene also has peripheral anti estrogenic action at the level of the endometrium and

cervical mucus, partly explaining the discrepancy in ovulation rates and pregnancy rates⁴.

Letrozole, a selective aromatase inhibitor, prevents the conversion of androgens to estrogen, thus releasing the hypothalamo-pituitary axis from the negative feed back of estrogen, resulting in an increase of FSH secretion from the anterior pituitary. The accumulated androgens in the ovary further increase follicular sensitivity to FSH¹⁵.

Importantly, unlike clomiphene citrate, letrozole is devoid of any anti estrogenic peripheral action. Letrozole is also cleared from the circulation more rapidly due to a shorter half life (48 hours) as compared to clomiphene citrate which may take up to 2 months due to its prolonged half life (2 weeks)¹⁶. Letrozole has been shown to be effective in ovulation induction in CC-resistant PCOS women¹⁷. Hyperinsulinemia, which is closely associated with PCOS, is thought to be one of the causative factors for CC resistance. The prevalence of insulin resistance in PCOS is close to 50%¹⁸. This could be one more reason for letrozole to be a better first-line drug compared to clomiphene citrate.

Multi-follicular development was statistically significantly higher in our study in cc group (CC 44.24%, Let 21.68%). This is expected and corroborated by number of studies^{19,20,21}. Letrozole resulted in mono-folliculogenesis in 78.32% of cases, which is optimal for ovulation induction in PCOS women. However, where multiple follicular development is needed, letrozole may be inadequate.

The mean endometrial thickness was slightly higher in letrozole group, 7.65±1.98 compared to CC 7.62±1.95. In a recent study by Banerjee *et al*²² 147 Indian women with PCOS were compared between letrozole (2.5 mg) Vs. clomiphene (100 mg). Mean endometrial development was 8.72±11.41 mm in letrozole and 8.78±1.16mm in CC group ($P= 0.004$). Mitwally and Casper⁶ found letrozole associated with greater endometrial thickness.

Badawy *et al.*(19) in their study of 438 patients with 1063 cycles, one of the largest studies comparing CC and letrozole, reported statistically significantly higher endometrial thickness in CC group (9.2±0.7) vs. letrozole (8.1±0.2, $P= 0.021$). Few studies have shown no significant difference between the two groups with regard to effect on endometrium^{23,24}.

Pregnancy rate per cycle was astonishingly high with letrozole in our study (20.55%) Vs. (7.42%). Requena *et al* (25) in their literature review looked at randomized trials comparing letrozole versus clomiphene as first line therapy and included four studies (Atay *et al* 2006; Bayar *et al* 2006; Sorabvand *et al* 2006; Badawy *et al* 2007) (26,20,27,19). The ovulation rate for letrozole in comparison with

clomiphene did not differ significantly (OR 1.7; 95% CI 0.66 - 2.09) nor did the pregnancy rate per patient (OR 1.37; 95% CI 0.70 - 2.71). However results need to be interpreted cautiously since the studies included were not statistically homogenous ($I^2>50\%$). Zeinalzaden *et al.*,(21) with 107 women reported slightly better pregnancy rates with letrozole; however, no statistically significant difference between the two groups.

In a meta-analysis by He and Jiang,(28) the clinical efficacy of letrozole was compared with clomiphene for ovulation induction in PCOS women. This is one of the largest meta-analysis of the subject published. Six RCTs involving 841 patients were analyzed. There were no significant differences in pregnancy rate, abortion rate, and multiple pregnancy rate between the two groups. The evidence from ovulation rate was not enough to support either of the drugs

CONCLUSION

Our study showed statistically significantly higher mono-follicular development and pregnancy rates when letrozole was used as ovulation induction drug in infertile PCOS women. However there is need for larger well designed randomized trials to generate robust data in order to establish the true potential of letrozole.

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