

Letrozole for Ovulation Induction in Clomiphene Resistant Women with Polycystic Ovarian Syndrome

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ABSTRACT

Objective To determine the frequency of successful ovulation induction with letrozole in infertile women with polycystic ovarian (PCO) syndrome who were resistant to clomiphene citrate.

Study design Descriptive case series.

Place & Duration of study Department of Gynaecology and Obstetrics ward-8, Jinnah Postgraduate Medical Center Karachi, from September 2009 to March, 2010.

Methodology Women between 20-40 year of age with history of PCO and primary infertility of at least one year duration who failed induction on clomiphene citrate for at least 2 months, were included in the study. After taking informed consent and counseling letrozole was given in a dose of 2.5 mg daily from day 3-7 of menstrual period. Patients were monitored by transvaginal ultrasound scan (TVS). The mean follicular diameter was noted on day 10, 12, 14, and 16. This was followed by HCG injection 10000 IU and serial monitoring of the follicles till 18mm size reached.

Results Sixty seven patients were selected. Mean age was 27.6 ± 3.3 year and mean duration of infertility was 4.3 ± 1.6 year. Fifteen (22.4%) of patients had infertility for 4 years, 13 (19.4%) had for 5 years and 12 (17.9%) for 6 years. Ovulation was successfully induced in 33 (49.3%) women.

Conclusion Letrozole can be used as a second line agent when there is resistance to clomiphene citrate, a first-line treatment, for induction of ovulation in women with polycystic ovarian syndrome.

Key words Polycystic ovarian syndrome, Infertility treatment, Clomiphene citrate, Letrozole.

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is the most commonly diagnosed female endocrinopathy affecting approximately 6% of women of reproductive age group.¹ About 55 – 75% of patients with PCOS are infertile due to chronic anovulation.^{1, 2} It is a clinical syndrome comprising of oligo / amenorrhea, obesity, infertility and hirsutism.³ Many treatment modalities have been proposed and implemented in an effort to circumvent the intrinsic block to ovulate.

Clomiphene citrate (CC), commonly used first line treatment for induction of ovulation, is successful in inducing ovulation in over 80% of women but pregnancy occurs in 30 to 40% of cases only.¹ It exerts unavoidable antiestrogenic effects on the endometrium and endocervix that explains the absence of pregnancy despite ovulation observed in some of the treated patients.^{4, 5} Traditionally gonadotrophins are the 2nd line treatment for patients who fail to conceive with CC, however gonadotrophins are associated with 30% to 40% risk of multiple gestation and ovarian hyperstimulation syndrome.⁶

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In the late 1990s, aromatase inhibitors specifically letrozole, which is indicated for the treatment of breast cancer, began to be used off label, to induce ovulation. It is associated with higher pregnancy

rates and avoid some of the negative effects often associated with CC.⁵ During letrozole treatment ovulation occurred in about 54% of cases and pregnancy in 25% of cases.⁶

Letrozole has been demonstrated to induce ovulation in patients who failed to ovulate with CC.⁷ Side effects of this drug are uncommon and include hot flushes, nausea and fatigue.⁸ This study was conducted to find out the success rate of letrozole for ovulation in infertile PCOS women as second line treatment who were resistant to CC.

METHODOLOGY:

This descriptive study was conducted at the Department of Gynaecology and Obstetrics ward-8, Jinnah Postgraduate Medical Center Karachi, from September 2009 to March, 2010. Patients were selected from the out-patient department. Women between 20-40 year of age with history of PCO and primary infertility of at least one year duration who failed induction on clomiphene citrate for at least 2 months, were included. Women with other causes of infertility like hyperprolactinemia, thyroid disease, known or suspected tubal factor infertility and history of chronic illness like tuberculosis and hypertension, were excluded.

After taking informed consent, women were counseled regarding treatment, dosage, effects and follow up. Letrozole was then given in the dose of 2.5 mg daily from day 3-7 of menstrual period. Patients were then monitored by TVS for mean follicular diameter (mm) on day 10, 12, 14, and 16. HCG injection 10000 IU, was given when at least one follicle measured 18 mm (mature follicle) and TVS was done 2 days after HCG injection to confirm ovulation by either disappearance of follicle, or an irregular follicle. All the information was entered on predesigned proforma. Statistical software (SPSS-

10.0) was used for data analysis. Frequency and percentages were calculated for ovulation induction. Mean \pm SD was calculated for age of the patients and duration of infertility. Stratification was done for age and duration of infertility.

RESULTS:

Sixty-seven patients were included in the study. The mean age of the study population was 27.6 ± 3.3 year. The range was 22 to 37 year. The mean duration of infertility was 4.3 ± 1.6 year with range of 2 to 8 year. Fifteen (22.4%) patients had history of infertility for 4 years and 13 (19.4%) had infertility for 5 years (table I). Ovulation was successfully induced by letrozole in 33(49.3%) cases of infertility.

The duration of infertility in relation to the age of study population was further stratified. Eleven (16.4%) patients were of 26 years, this was followed by 10 (14.9%) of 27 year and 8 (12%) patients of 25 year. Out of 11 patients of 26 years 4 (36.4%) had infertility for 4 years, 3 (27.2%) had for 2 years and 2 (18.2%) had for 3 years. The highest number of patients (n=7, 21%), who had successful ovulation were of 26 year, this was followed by 4 (12%) in each of the age groups of 24 year, 25 year, 27 year and 30 year.

DISCUSSION:

Anovulation is a cause of infertility in 30-40% of cases.⁹ For the treatment of infertility due to anovulation various methods of ovulation induction are available.¹⁰ In polycystic ovarian syndrome pharmacological intervention of ovulation is often used. In addition there are several methods in use by virtue of which ovulation may be induced. This include methods for losing weight including various exercises and surgical intervention like ovarian drilling with laparoscopic approach.¹¹ The pharmacological compound commonly used include

Table I: Duration of Infertility

Duration (Year)	Frequency (n)	Percentage (%)
2	10	14.9%
3	12	17.9%
4	15	22.4%
5	13	19.4%
6	12	17.9%
7	03	4.5%
8	02	3.0%
Total	67	100%

antiestrogens drugs and human gonadotrophins. Other infrequently used agents are gonadotrophin releasing hormones (GnRH) given in a pulsatile fashion and GnRH agonist. More recently researchers have tried GnRH antagonists. Insulin sensitizers and aromatase inhibitors are also available in contemporary times.¹² Clomiphene citrate is the preferred treatment agent in patients with PCOS. In properly selected patients this drug has shown beneficial effects. The cumulative pregnancy rate in such cases may approach that of normal women. Clomiphene citrate is a first line treatment of infertile anovulatory women.^{13,14} Although the treatment induces ovulation in most women, only one in four achieve uncomplicated pregnancy after treatment over several cycles. During recent years several clinics have started to use aromatase inhibitors for ovulation induction.^{15,16}

Aromatase inhibitors suppress the biosynthesis of estrogen. This inhibits the negative feedback on the hypothalamic–pituitary system.¹⁷ This leads to increased in secretion of FSH. FSH can then lead to follicle selection and maturation.¹⁸ Letrozole is the third generation compound. It has been introduced recently for ovulation induction in anovulatory PCOS women resistant to clomiphene citrate. It is also used when there is inadequate endometrial thickness during clomiphene treatment.¹⁹ This compound was used in present study.

Mitwally conducted a comparative study. In that study 2.5mg letrozole was used daily from day 3 to 7 of the menstrual cycle. Ovulation rate in that study was 75% (nine of 12 cycles). In other group that was treated with clomiphene, ovulation was noted in eight of 18 cycles (44.4%). The endometrium on the day of HCG administration was found thicker in the letrozole group.²⁰ In another study pregnancy was reported in three (25%) patients treated with letrozole.²¹ Letrozole was found to be more effective than anastrozole in a recent study. This is another aromatase inhibitor. Ovulation rate was 84.4% with letrozole and 60% with anastrozole. Similarly pregnancy rate per cycle was 18.8% and 9.7% respectively in 22 anovulatory women with PCOS.²²

In a study by Dulgi AM et al mean age of patients treated with letrozole was 27.1 ± 0.9 year and mean duration of infertility was 2.2 ± 0.7 year.²³ This compared well with the results of the current study. Rossing MA et al in their study found that ovulation was achieved by letrozole in 62% of PCOS patients resistant to clomiphene citrate, and pregnancy occurred in 12.2%.²⁴ In our study ovulation induction rate with letrozole in PCOS patients resistant to

clomiphene citrate was 49.3%.

CONCLUSION:

Letrozole was an effective second line agent when there is resistance to clomiphene citrate used as first-line treatment, for induction of ovulation in women with PCOS.

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