

## SHORT COMMUNICATION

## Experience of Using Letrozole as a First-Line Ovulation Induction Agent in Polycystic Ovary Syndrome (PCOS)

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**Abstract:** *Objectives:* To study the effects of aromatase inhibitor- letrozole, as a first-line ovulation inducing agent in anovulatory infertility due to PCOS (Polycystic ovary syndrome). *Materials & Methods:* This prospective study was conducted among 106 Women with PCOS (total 204 cycles). Letrozole was given as 2.5 mg. twice daily from day3 to day7 of menstrual cycle. Ultrasound folliculometry was started from day 8 onwards to monitor follicular development, ovulation & endometrial thickness. Timed intercourse was advised 24 hours after the leading follicular diameter reached  $\geq 17$  mm. in size till 12 hours post ovulation. Pregnancy detection was done by urine for pregnancy test once the menstruation was overdue & later confirmed by transvaginal sonography. *Results:* Out of 106 women, 72 women ovulated (67.9% ovulation rate), 29 women conceived (27.3% pregnancy rate), only 2 patients had miscarriage (1.8%). Over 204 cycles, per cycle pregnancy rate was 14.2%, & spontaneous ovulation rate was 35.2%. Average endometrial thickness on the day of documenting ovulation was 10.1  $\pm$  0.3 mm. None had developed ovarian hyper stimulation syndrome or multiple gestations. *Conclusion:* This study indicates letrozole may safely be considered as an effective & simple first-line ovulation induction agent using minimal resources in anovulatory infertility due to PCOS.

**Key Words:** Letrozole, ovulation induction, PCOS, Infertility.

### Introduction

Polycystic ovary syndrome (PCOS) is a silent epidemic; a leading cause of infertility in women due to anovulation. The induction of ovulation in women with PCOS is a complex issue. The concept of using third generation non-steroidal aromatase inhibitor (Letrozole) as a method of ovulation induction has been extensively investigated by several research groups and letrozole appears to be effective, safe mode of treatment [1-4]. Letrozole suppresses the biosynthesis of estrogen by blocking the conversion of androgens to estrogen from all sources. This in turn reduces the negative feedback effect of estrogen at the hypothalamic pituitary axis, thereby increasing gonadotropin secretion and resulting in stimulation of ovarian follicles. Because letrozole does not antagonize estrogen receptors in brain, the initiation of follicle growth producing increasing concentrations of both estradiol and inhibin results in a normal secondary feedback loop that limits FSH response, thereby avoiding the risk of high multiple ovulation and ovarian hyperstimulation syndrome (OHSS). Aromatase Inhibitors (AI) also acts locally in the ovary to increase follicular sensitivity to FSH by resulting accumulation of intraovarian androgens. Letrozole, having a very short half life ( $\leq 45$  hours) is quickly cleared

from the body (mainly by the liver) is therefore less likely to adversely affect the endometrium and cervical mucus [1, 5-6]. These knowledge prompted us to use letrozole as a first-line ovulation induction agent in PCOS (diagnosis based on Rotterdam ESHRE\ASRM revised 2003 consensus on diagnostic criteria) [7] in a resource poor set up. Another aim was to evaluate letrozole as a proposed ovulation induction agent for use by the community gynecologists who may not have strict monitoring facility like measuring serum estradiol level or beta hCG & transvaginal sonography (TVS) so that heavy socio-economic burden of infertility treatment can be lessened.

*Objectives:* To assess the possibility of use of AI (Letrozole) as a first-line treatment for ovulation induction in PCOS cases in set-ups where intense monitoring is not possible. Outcomes were measured to determine the success of therapy in terms of ovulation rate, pregnancy rate, endometrial thickness, miscarriage rate and development of severe adverse effect like OHSS, multiple gestations.

### Materials and Methods

This prospective study was conducted in women attending the Dept. of Obstetrics and Gynecology; KPC Medical College, Jadavpur, Kolkata over a period of 3 years (from March 2007 to February 2010). 106 women aged between 23 to 32 years with primary infertility for a period of 2 to 5 years because of anovulation related to PCOS, were recruited for study after taking informed consents from the couples. Couples with any other significant sub fertility factor in either of the partner detected by prerecruitment investigations, were not included in this study. Only fresh (not treated previously) cases were recruited. The Ethics Committee of the hospital approved this study. Each woman received letrozole therapy (Letoval, SUN Pharmaceutical Spectra division, India) as 2.5 mg. twice daily (5 mg. per day) from 3<sup>rd</sup> day of menstrual cycle up to 7<sup>th</sup> day (5 days in total). Ovulation and endometrial thickness were monitored by folliculometry by the same observer from 8th day onwards. Timed intercourse was advised 24 hours after measuring dominant follicle of  $\geq 17$  mm. [8] till 12 hours post ovulation. Total cycles of treatment was 204. Urine for pregnancy test was done once the menstruation was overdue and later confirmed by TVS showing presence of gestation sac with cardiac activity at 7<sup>th</sup> week of gestation [8].

### Results and Analysis

The primary outcome measures were number of mature follicles, ovulation rate, endometrial thickness (in mm.), and development adverse effect if any. Secondary outcome measures were the pregnancy rate and miscarriage rate. Table 1-3 shows the results of the present study. Out of 106 women, total 72 women ovulated (67.9%) of which 36 women ovulated in their first treatment cycle. Number of follicle developing  $\geq 17$ mm. was 1.3(+0.2). In 204 treatment cycles, spontaneous ovulation (i.e. not using triggering methods like hCG injection) rate per cycle was 35.2%. The endometrial thickness on the day of documenting ovulation was found to be between 9.8 to 10.4 mm. Out of 106 cases, 29 women became pregnant (27.3%)

Table-1: Data of present study as per no. of cases	
Parameters	Number (%)
Total no. of cases	106
Ovulation	72 (67.9%)
Pregnancy	29 (27.3%)
Miscarriage	2 (1.8%)

and per cycle pregnancy rate was 14.2%. As good as 14 women conceived in the first treatment cycle out of 106 women. There were 2 cases of early pregnancy loss (1.8%). None had developed multiple pregnancy or OHSS.

Table-2: Data of present study as per treatment cycles	
Parameters	No. (%)
No. of treatment cycles	204
Ovulation	72(35.2%)
Pregnancy	29(14.2%)

Table-3: Results of folliculometry in present study	
Parameters	Number/ Thickness
Follicle development $\geq 17$ mm	1.3 $\pm$ 0.2
Endometrial thickness on the day of documenting ovulation	10.1 $\pm$ 0.3 mm

### Discussion

This is a clinic-based study where letrozole has been used as a first-line ovulation-inducing agent in infertility due to PCOS. Letrozole has been claimed to have several advantages as an ovulation-inducing agent [1] and they are as follows-

- 1) High pregnancy rate.
- 2) Monofollicular ovulation- lesser chance of OHSS & Multiple gestation.
- 3) 100% bioavailability after oral administration and rapid clearance from the body, so less likely to have anti estrogenic effect on endometrium and cervical mucus quality.
- 4) No accumulation of the medicine or its metabolite.
- 5) Low cost of treatment.

Study conducted by Ganesh et al [8] reported overall pregnancy rate of 23.39 % by using letrozole whereas in our study it is 27.3%. Increased success rate (even not using intrauterine insemination), probably because our patient population was younger (Mean age 30.2 years vs. 27.5 years). Problems & disadvantages associated with the use of clomiphene citrate (CC), the alternative drug approved for ovulation induction for decades, are lower pregnancy rate despite high ovulation rate [9-11], high miscarriage rate of 13-25% [12-13] & high CC doses have been associated with OHSS & multiple pregnancy [12]. Evidence based medicine have shown that there is very little role of any adjuvant in improving pregnancy rates with CC treatment [14]. Here lies the quest for searching a suitable first-line agent. Casper [3] has stated that letrozole has a potential role as a first-line oral therapy for ovulation inductions in women with PCOS. Our study also shows that using 5 mg of letrozole per day for 5 days in each cycle (total 204 cycles), there were comparable ovulation and pregnancy rates and not a single case of multiple pregnancy and OHSS. The present study also shows that number of follicle reaching the diameter of  $\geq 17$ mm. per cycle was 1.3 ( $\pm 0.2$ ). Bayar et al [15], Atay et al [11] had reported monofollicular development in their studies. We therefore propose that follicular monitoring is not essential in all

cases and this can further reduce the cost of therapy. Further studies should be aimed at finding out the optimum regimen for administering letrozole- long protocol, single dose protocol etc.

### Conclusion

Based on the evidence revealed in our study, we believe that the aromatase inhibitor Letrozole is an efficient, safe ovulation induction agent in WHO Type II anovulatory infertility like PCOS. Letrozole can be used as a simple inexpensive first-line treatment so that stigma of Clomiphene Citrate Resistance may not have to be faced. We also propose that with proper case selection for letrozole therapy, close monitoring by folliculometry is not essential which makes it simpler & cheaper. Further research on use of letrozole either as long protocol, or single dose protocol may lead to LETROZOLE replacing CC as primary treatment for ovulation induction. Letrozole appears to come as a boon for the Community Gynecologists having limited infrastructure.

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