

## The Effect of Letrozole in Induction of Ovulation in Clomiphene Resistant Patients

Robab Davar, M.D.<sup>1</sup>, and Abbas Aflatoonian M.D.<sup>2</sup>

<sup>1</sup> Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences. Yazd, Iran.

<sup>2</sup> Madar Hospital, Yazd, Iran.

**Background:** In patients with anovulatory infertility the first choice of treatment for ovulation induction is an antiestrogen, most commonly clomiphene citrate (CC). However, 20-25% of the women are resistant to CC and do not ovulate perhaps due to antiestrogenic mechanism of the CC action, which involves long-lasting estrogen receptor (ER) depletion.

**Objective:** The objective of the study was to mimic the action of CC without depletion of ERs by the administration of an aromatase inhibitor letrozole in a selected group of Poly Cystic Ovary (PCO) patients who demonstrated failure to ovulate after treatment with CC.

**Materials and Methods:** 20 patients with anovulation due to polycystic ovary syndrome (PCOS), who had previously inadequately responded to CC were selected for study. The aromatase inhibitor letrozole was administered orally in a dose of 2.5 mg on days 3-7 of the menstrual cycle. Then, occurrence of ovulation, endometrial thickness, and pregnancy rates were determined.

**Result(s):** Only one patient had one dominant follicle (1.8 cm diameter) on day 14 of the cycle (estradiol = 200 pg/ml). IUI was done; however, no pregnancy took place. In the remaining cases, several sonographies were done between days 9 to 15 of the cycle; however, all cycles were cancelled due to absence of a dominant follicle (>1.4 cm).

**Conclusion(s):** Our study did not confirm the favorable effect of letrozole for induction of ovulation in patients with clomiphene resistant PCO.

**Key Words:** Letrozole, Clomiphene failure, PCOS

### Introduction

In women with anovulatory infertility, the first choice of treatment for induction of ovulation is an antiestrogen, most commonly clomiphene citrate (CC) (Shoham and Weissman, 1998; Frank, 1995). However, 20-25% of the women are resistant to CC and do not ovulate. In addition, clinical data have revealed a discrepancy between ovulation and conception rates during CC treatment and a higher incidence of miscarriage in conception cycles (Frank, *et al.*, 1985; Hull, 1992). These observations have been attributed to the antiestrogenic mechanism of the CC action, which involves long-lasting estrogen receptor (ER) depletion. It also appears that CC accumulates in the body because of its long half-life. As a result, CC may have a negative effect on the quality and

quantity of the cervical mucus, on endometrial development, and on other as yet undetermined infertility factors (Gysler, *et al.*, 1982; Hammond, *et al.*, 1983).

With the failure of CC, gonadotropin preparations such as HMG or pure FSH have been used as a second-line treatment for ovulation induction. In women with PCOS, because of the high sensitivity of the ovaries to gonadotropin stimulation, treatment with HMG or pure FSH induces several ovulatory follicles, leading to the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (Kettel *et al.*, 1993).

A group of highly selective aromatase inhibitors has been approved for use in postmenopausal women with breast cancer to suppress estrogen production. These aromatase inhibitors have a relatively short half-life compared with CC; therefore, they would be eliminated from the body rapidly (Lipton, *et al.*, 1995; Iveson, *et al.*, 1993). In addition, because ER down-regulation does not occur, no adverse effects on estrogen target tissue,

#### Corresponding Author:

Dr. Robab Davar. Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

E-mail: r\_davar@yahoo.com

as observed in CC-treated cycles, would be expected. We hypothesized that it may be possible to mimic the action of CC without depletion of ERs by the administration of an aromatase inhibitor in the early part of the menstrual cycle. This would result in the escape of the hypothalamic/ pituitary axis from estrogenic negative feedback, increasing gonadotropin secretion and resulting in stimulation of ovarian follicle development.

Therefore, the objective of this study was the administration of aromatase inhibitor letrozole in a selected group of PCO patients who demonstrated failure to ovulate after treatment with CC.

### Materials and Methods

This study was performed as a clinical trial at the Research and Clinical Center for Infertility, and Madar private Hospital in Yazd.

The patients consisted of 20 infertile women with PCOS who were resistant to CC and candidate for IUI or timed intercourse. If ovulation and a normal luteal phase are not achieved after 3 cycles of increasing doses of clomiphene, the patients are considered to be resistant to clomiphene.

In all patients, letrozole (Femara; Novartis pharma AG, Switzerland) treatment was given orally at least 2 months after the last CC cycles, in a dose of 2.5 mg/day, from days 3 to 7 of the menstrual cycle. Patients were followed by follicular monitoring with transvaginal ultrasound. Our plan was the serial measurement of estradiol and endometrial thickness on the day of HCG injection, then administration of HCG (10000 IU, IM) when at least one follicle  $\geq 20$ mm will develop. Chemical pregnancy must be assessed by measurement of  $\beta$ -HCG and clinical pregnancy by detection of fetal heart beat on sonography.

Since no dominant follicle developed in all patients except one, their measurements was not done. In one patient who developed one dominant follicle timed intercourse was suggested.

### Results

Mean age of patients was  $29.1 \pm 4.07$  and duration of infertility was  $9.3 \pm 3.4$ .

All patients were PCOS and had inadequate response to clomiphene citrate in previous cycles. Of 20 patients who received letrozole, only one developed one follicle 18mm on day 14, and in others, in spite of continue by monitoring vaginal sonography until 15<sup>th</sup> day of the cycle no dominant follicle was observed. Therefore other monitoring

as measurement of estradiol and endometrial thickness was not done and as a consequence, we did not take the data as the number of follicle, estradiol level and thickness of endometrium on the day of HCG injection. For the patient who developed one dominant follicle timed intercourse was suggested, but no pregnancy occurred.

### Discussion

Several methods for ovulation induction have been suggested in patients with PCOS. Tao and Dai. (1999) suggested the application of compound cyproterone acetate. These patients used compound cyproterone acetate for 4-6 months, then induction of ovulation was done with CC or HMG. Ovulation and pregnancy rates were higher in these patients.

Another study was done by Mitwally and Casper (2002). They included 12 patients with unexplained infertility with a low response to ovarian stimulation with FSH in at least two cycles. Patients were offered letrozole as an adjuvant treatment with FSH injection to improve ovarian response to FSH stimulation.

Letrozole was given at a dose of 2.5mg from day 3 to 7 of the menstrual cycle and FSH start on day 7 at a dose of 50-225 IU/day. Four patients achieved pregnancy during letrozole plus FSH treatment cycles.

Metformin also increases ovulation and pregnancy rate in patients with PCO disease who are clomiphene resistant (Tao and Dai, 1999; David, *et al.*, 2001). In another study, induction of ovulation was done in 59 clomiphene resistant PCO patients by one of two protocols: FSH only and pulsatile GnRH+FSH. Pregnancy rate was 37.54% and 22%, respectively. They concluded that the highest rate of pregnancy was achieved with GnRH+FSH (Donesky and Adashi, 1996). With respect to antiestrogenic effects of clomiphene on target organs such as cervix and endometrium, use of a drug that can mimic clomiphene effects in inducing ovulation, without antiestrogenic effect seems to be useful in such patients.

Letrozole is a nonsteroidal competitive inhibitor of aromatase enzyme that selectively inhibit gonadal steroidogenesis. It also has no effect on mineral corticoids and glucocorticoids synthesis in adrenal (Deleo and Imarca, 1999). This drug is used in advanced breast cancer in postmenopausal patients extensively. Women with ovulatory disorders who are resistant to standard doses of CC generally become candidates for gonadotropin therapy. However, severe OHSS and the high risk

of multiple pregnancies are major disadvantages of gonadotropin treatment, especially in young women with PCOS.

We hypothesized that letrozole administration in the early part of the menstrual cycle would release the pituitary/hypothalamic axis from estrogenic negative feedback, similar to the effect of CC but without ER down-regulation and the adverse endometrial and cervical mucus effects seen with CC. Mitwally *et al* (2001), used letrozole in 22 patients who were clomiphene failure in a dose of 2.5 mg/day from days 3 to 7 of the menstrual cycle. Ovulation occurred in 75% of the patients and pregnancy in 25%. Endometrium was thicker in letrozole group. They selected patients with no ovulation and/or endometrial thickness  $\leq$  0.5 cm in previous cycles. We used letrozole in PCO patients that ovulation and a normal luteal phase were not achieved after 3 cycles with increasing doses of clomiphene. In contrast to their study, no follicular development was occurred in 95% of our patients. Therefore, letrozole had a very limited effect on ovulation in these patients.

Recently Fatemi *et al.* (2003), compared endocrinological environment of cycles stimulated with CC or letrozole. Fifteen patients undergoing IUI received from day 3 to 7 of the cycle either letrozole 2.5 mg/day or CC 100mg/day. Estrogen, progesterone and number of follicles were compared in two groups. Significantly lower estradiol concentration and fewer follicles are observed in cycles stimulated with letrozole compared to CC.

From the existing literature, it appears that use of an aromatase inhibitor alone to induce or augment ovulation will continue to be an exciting area of research future. In particular, the dosage and timing of administration (late luteal versus early follicular) of an aromatase inhibitor for ovulation induction should be optimized ( Bulun 2003).

Our results showed that the favorable response of letrozole was not demonstrated in our patients.

The poor response to letrozole in our patients may be constitutionally, or this dose is not enough. Therefore, in future, higher doses of letrozole (e.g. 5mg/day) or the addition of gonadotropin to it could be studied.

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