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A RANDOMIZED TRIAL OF SUPEROVULATION WITH TWO DIFFERENT DOSES OF LETROZOLE

Gynaecology

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ABSTRACT

Objective: The aim of this study was to evaluate the effects of either a 2.5-mg or a 5-mg daily dose of letrozole in women undergoing superovulation and intrauterine insemination (IUI).
Design: Prospective randomized trial.
Setting: Academic teaching hospital.
Patient(s): Women 40 years old, with patent fallopian tubes and infertility of 1 year in duration.
Intervention(s): Patients were randomized into either a 2.5-mg dose of letrozole (34 patients) or a 5-mg dose of letrozole (38 patients) daily for 5 days. When the leading follicle reached 18 mm in diameter, ovulation was triggered by an injection of hCG and IUI was performed 24 and 48 hours later.
Main Outcome Measure(s): The number of follicles, endometrial thickness, and pregnancy rate.
Result(s): Compared with those treated with 2.5 mg of letrozole, the total number of follicles was significantly higher in patients receiving 5 mg of letrozole. No difference in the endometrial thickness was found between the two groups. The pregnancy rate per cycle in patients receiving 5mg of letrozole was statistically higher than in patients receiving 2.5 mg of letrozole (26.3% vs. 5.9%, *P* .05). No multiple pregnancies occurred.
Conclusion(s): Compared with the daily dose of 2.5 mg, 5 mg of letrozole is associated with more follicles and a higher pregnancy rate. It appears that 5 mg daily for 5 days is a preferable letrozole dose for superovulation

KEYWORDS

Ovulation, superovulation, controlled ovarian hyperstimulation, aromatase inhibitor, letrozole

Introduction

One of the treatments of unexplained infertility or mild male factor infertility is controlled ovulation hyperstimulation of superovulation with clomiphene citrate (CC) and intrauterine insemination (IUI) (1–3). Gonadotropin has also been used; however, it is associated with high risk of ovarian hyper-stimulation and multiple pregnancies (4, 5).

Letrozole is a third-generation aromatase inhibitor. It was postulated that blocking estrogen production by inhibiting aromatization would release the hypothalamic/pituitary axis from estrogenic negative feedback (6 – 8). As a result, FSH secretion increases, stimulating the development of ovarian follicles (7, 8). Preliminary studies report that it is indeed useful in inducing ovulation and in superovulation. The ideal daily dose of letrozole, however, remains unknown.

In a small study of 12 anovulatory women with polycystic ovary syndrome, 2.5 mg of letrozole daily for 5 days appears to be effective. We recently reported the results of a ran-domized trial of 238 cycles of superovulation with 7.5 mg of letrozole or 100 mg of CC daily for 5 days in women with idiopathic infertility. The pregnancy rates in both groups were similar, but the miscarriage rate in the CC-treated cycles was higher (9). The purpose of our study was to evaluate the effects of 2.5 or 5 mg of letrozole daily in women undergoing superovulation and IUI.

MATERIALS AND METHODS

Between March 2016 and January 2017, we studied 72 patients who underwent superovulation and IUIs at Sheth V.S. General Hospital. Patients were randomized into treatment with a letrozole dose of 2.5 mg or 5 mg daily. Randomization was completed using a computer-generated random table. The hospital Research Ethics Board approved the study. Study participants were counseled, and informed consent was obtained before randomization.

The inclusion criteria were patients with infertility of at least 1 year, menstrual cycle between 25 to 35 days, patent tubes on the hysterosalpingogram, and normal semen anal-ysis of the male partners. Both treatments were administered from day 3–7 of spontaneous cycle. Transvaginal ultrasound examinations were performed on day 3 of the cycle to confirm the absence of ovarian cysts, before starting the medication. Subsequent ultrasound scans were performed on day 9 of the menstrual cycle and daily after the mean diameter of the largest follicle reached 16 mm. At each ultrasound scan, the internal diameter of each visible follicle was measured in three dimensions, and the average diameter was then calculated. Additionally, the endometrial thickness, defined as the maximum distance between the echogenic interfaces of the myometrium, was measured in the plane through the central longitudinal axis of the uterus.

The same two ultrasonographers performed ultrasound examinations. When the mean diameter of at least one fol-licle had reached 18 mm, 10,000 IU of hCG was administered SC to trigger ovulation and IUI was performed 24 and 48 hours later. Serum *b*-hCG was measured a few days after the patients missed their periods.

The pregnancy rate was calculated based on a positive urine pregnancy test or serum *b*-hCG of 10 mIU/mL and the presence of intrauterine gestational sac seen by the ul-trasound. We evaluated the number of follicles, endometrial thickness, and pregnancy rate. Only the first treatment cycle was included in the analysis.

TABLE 1Characteristics of patients undergoing superovulation with 2.5 mg or 5 mg of letrozole daily.

				Patient group
		Letrozole 2.5 mg		Letrozole 5 mg
No. of patients	34	38		
Age (y)	31.8	0.3	31.8	0.7
Duration of infertility (y)	2.7	0.3	3.0	0.4
FSH (IU/L)	4.5	0.3	4.9	0.3
LH (IU/L)	5.0	0.5	5.1	0.6
E_2 (pmol/L)	155	14	144	11
Progesterone (nmol/L)	40.1	7.5	36.1	5.3

Statistical Analysis

The normality of data distribution was tested using the Shapiro-Wilks test. Because the data were not normally distributed, we used the Mann-Whitney U test. Chi-square tests were used to compare proportions. Results are ex-pressed as mean and standard error of the mean. The differ-ences are considered statically significant if P .05.

RESULTS

The mean age, duration of infertility, basal FSH, LH, E2, and mid-luteal progesterone in both groups of patients were similar (Table 1). Of the total 72 patients, 34 patients were randomized into the 2.5-mg group and 38 others into the 5-mg group. One patient developed severe side effects to the 2.5-mg dose of letrozole (i.e., severe headache, hot flushes, and nausea); the treatment was discontinued, and she was excluded from the study.

Table 2 depicts the results of superovulation with two different doses of letrozole. There was no difference in the duration to reach a dominant follicle and the endometrial thickness between the two letrozole groups. The total num-ber of follicles was statistically higher in the letrozole 5-mg group compared with the letrozole 2.5-mg group. The preg-nancy rate per cycle was statistically higher in the letrozole 5-mg group (26.3%) compared with the letrozole 2.5-mg group (5.9%). No multiple pregnancies or ovarian hyper-stimulation were encountered.

DISCUSSION

Compared with CC, letrozole does not have or has a minimal peripheral antiestrogen effect. This is related to the short half-life of letrozole. In theory, it should lead to a higher pregnancy rate and lower miscarriage rate than those of CC. Preliminary studies of letrozole employed a daily dose of 2.5–7.5 mg for 5 days or a single dose of 20 mg orally. The dose of 2.5 mg was adopted from a daily dose of letrozole as an adjunct hormonal treatment for breast cancer. The 5-day treatment was taken from the 5-day CC regimen.

Administration from day 3–7 of the cycle allows sufficient time for letrozole to be cleared from the body, leaving only negligible levels close to the time of ovulation. The ideal dose of letrozole for ovulation induction or superovulation is still unknown.

Fisher et al. conducted a small, randomized study in 19 normal healthy ovulatory volunteers not desiring pregnancy (10). They randomized the patients to receive either 2.5 mg of letrozole daily (9 patients) or 50 mg of CC daily (10 patients) on day 5–9. The results were compared with un-treated cycles of the same patients. The mean number of mature follicles in the untreated cycles was 1, 2.2 in the CC cycles, and 1.7 in the letrozole cycles. The endometrial thickness was comparable between the untreated and treated cycles. The CC treatment resulted in an increase in estradiol (E2) levels, whereas the levels in the letrozole group were lower than in the natural cycles.

In the present study, we compared the effects of daily doses of either 2.5 mg or 5 mg of letrozole. We found no difference in the endometrial thickness between the two groups. However, the pregnancy rate was higher in the letrozole 5-mg group than the 2.5-mg group. This was re-lated to a higher number of follicles in the letrozole 5-mg group. If mono-ovulation is desirable in ovulation induction, in superovulation we prefer to have a higher number of follicles, and the 5-mg daily dose appears to be proper dose.

Letrozole has also been used in combination with gonad-otropin for superovulation (8, 11). We previously compared superovulation with gonadotropin, or a combined regimen of gonadotropin and letrozole (5 mg daily on day 3–7) (11). Gonadotropin was started on day 3 of the cycle as well ("overlapping approach"). Patients treated with a combined regime required less gonadotropin and developed more follicles larger than 14 mm, but had thinner endometrium. However, no significant difference was found in the preg-nancy rates between the two groups (gonadotropin 20.9%, gonadotropin/letrozole 21.6%).

In a study using a sequential approach with letrozole (2.5 mg/day) from day 3–7 and FSH (50 –225 IU/day) from day 7 of the cycle, the authors reported a pregnancy rate of 21% in three cycles (8). In this study, the endometrial thickness in both groups was similar. These preliminary results suggest that the addition of letrozole to gonadotropin decreases go-nadotropin requirements, increases the number of preovula-tory follicles, and possibly decreases endometrial thickness without a negative effect on the pregnancy rates.

Despite the encouraging experience of letrozole as an adjunct treatment in ovulation induction and superovulation, there is a paucity of information on its use in IVF programs. Two studies evaluated the effects of letrozole in poor re-sponders (12, 13). The authors concluded that its use is associated with a reduced amount of gonadotropin without any effects on implantation and pregnancy rates.

The results of the present study demonstrate that, com-pared with the daily dose of 2.5 mg, 5 mg of letrozole is associated with more follicles and higher pregnancy rate. It appears that 5 mg daily for 5 days is a preferable letrozole dose for superovulation.

TABLE 2 Results of superovulation with 2.5 mg and 5 mg of letrozole daily.

			Patient group		
		Letrozole 2.5 mg	Letrozole 5 mg	*P* value	
No. of patients	34	38			
No. of days required to achieve follicular maturity	11.4	0.4	11.7	0.4	NS
No. of follicles 14 mm on day of hCG administration	1.3	0.1	2.0	0.1	.001
No. of follicles $18 mm on day of hCG administration	1.1	0.0	1.3	0.1	.05
Endometrial thickness (mm)	7.5	0.3	7.8	0.3	NS
Pregnancy rate per cycle started (%)	5.9 %	26.3%		.05	

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