Letrozole vs. clomiphene citrate in patients with ovulatory infertility

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Objective: To compare the effectiveness of letrozole and clomiphene citrate (CC) in ovulatory patients with borderline male factor infertility, early stage endometriosis, and unexplained infertility.
Design: Prospective quasi-randomized trial.
Setting: University infertility clinic.
Patient(s): Forty-six consecutive patients with ovulatory infertility were recruited. Twenty-five patients (67 cycles) were given CC and 21 patients (52 cycles) were given letrozole. Both drugs were given orally on days 3–7 of menses.
Intervention(s): Letrozole, CC, ovulation induction, IUI, timed intercourse.
Main Outcome Measure(s): Number of follicles, endometrial thickness, and pregnancy rates.
Result(s): The median serum E_2 concentration on the day of hCG administration in the letrozole and CC groups were 191.5 pmol/L and 476.0 pmol/L, respectively. The median endometrial thickness on the day of hCG were 8 mm in both groups. Ovulation occurred in 81% (42/52) of the letrozole-treated and 85% (57/67) of the CC-treated patients. Pregnancy rate (PR) per cycle was 9% (5/52) in the letrozole group and 12% (8/67) in the CC group.
Conclusion(s): Letrozole and CC have comparable effectiveness in ovulatory patients with borderline male factor infertility, early stage endometriosis, and unexplained infertility. (Fertil Steril® 2006;85:1045–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: Letrozole, clomiphene citrate, ovulation induction, ovulatory infertility

Controlled ovarian hyperstimulation (COH) with or without IUI is often used for the treatment of unexplained infertility, early stage endometriosism and borderline male factor infertility (1, 2). Clomiphene citrate (CC), requiring minimal monitoring, is often used for this purpose (2).

Aromatase inhibitors have originally been developed for the treatment of breast cancer. Aromatase is a cytochrome P-450 hemoprotein and catalyzes the rate-limiting step in the production of estrogens (E) (i.e., conversion of androstenedione [A] and T to estrone (E_1) and E_2, respectively, by three hydroxylation steps) (3). Letrozole, a triazole derivative, is a highly potent, selective, competitive, and reversible aromatase inhibitor. Letrozole has been recently proposed to be used as an alternative to CC as a first-line treatment agent to induce ovulation in anovulatory and ovulatory infertile patients (4).

The aim of this study was to compare the effectiveness of letrozole and CC for ovulation induction in patients with unexplained infertility, early stage endometriosis, and borderline male factor infertility.

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MATERIALS AND METHODS

This prospective quasi-randomized trial was performed in Zonguldak Karaelmas University Hospital, Zonguldak, Turkey. Fifty consecutive patients with unexplained infertility, early stage endometriosis, and borderline male factor infertility from January 2002 to January 2003 were included. Inclusion criteria included infertility lasting more than 1 year, documentation of ovulation with midluteal serum P levels exceeding 5 ng/mL (conversion factor 3.18 nmol/L), normal hormonal profile (TSH, PRL, T, and DHEAS), and day 3 FSH <12 IU/L. The diagnosis of unexplained infertility was based on a normal semen analysis using World Health Organization criteria (5), documentation of ovulation with midluteal serum P level exceeding 5 ng/mL, normal hysterosalpingography, and diagnostic laparoscopy. Ovulatory patients with stage I or II endometriosis and normal semen analysis were categorized as early stage endometriosis patients. The criteria for borderline male factor infertility were as follows: sperm concentration <10 million/mL, motility <20% (6), and morphology using strict criteria <4% (7).

Patients were randomized to CC (n = 25) or letrozole (n = 25). A quasi-randomization method was used. Based on the attendance order, patients with odd numbers were prescribed letrozole and those with even numbers were given CC. Neither the patients nor the physicians were blinded in any of the groups. Letrozole (Femara; Novartis Pharma AG

TABLE 1

Demographic features and ovarian reserve of the letrozole and CC-treated groups.

Variable	Letrozole	Clomiphene citrate	*P* value
No. of patients	21	25	
No. of cycles performed	2 (1–4)	3 (1–5)	.61
Female age (y)	31 (23–39)	31 (24–39)	.66
Duration of infertility	7 (3–16)	3 (3–13)	.01
Day-3 FSH (mIU/mL)	7 (3–12)	6 (3–11)	.11
Day-3 E_2 (pg/mL)	40 (29–83)	48 (26–86)	.06

Note: Values are median (range).

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Basle, Switzerland) and CC (Gonaphane, Organon, Santa Farma Ilaç Sanayi, Sirkeci, Istanbul, Turkey) were given orally in doses of 2.5 mg/day and 100 mg/day, respectively, from menstruation days 3–7. Patients were monitorized with transvaginal ultrasonography and serial measurements of E_2 starting on day 7 of the cycle. Human chorionic gonadotropin (Pregnyl, Organon, Santa Farma Ilaç Sanayi, Sirkeci, Istánbul, Turkey) at a dose of 10,000 IU was used to trigger ovulation when at least one follicle exceeding 18 mm in diameter was noted.

Intrauterine insemination was performed in patients with borderline male factor infertility both in the letrozole (n:27) and CC (n:36) groups. Timed intercourse was recommended in the remaining patients in both groups. Double IUI was performed 24 and 48 hours after administration of hCG. Ovulation was assumed to have occurred when midluteal serum P exceeded 5 ng/mL.

Intra-assay and interassay coefficients of variations of FSH, E_2, and P were as follows: FSH (analytical sensitivity: 0.1 mIU/mL, intra-assay coefficient of variation [CV]: 1.90%, interassay CV: 2.11%), E_2 (analytical sensitivity: 15 pg/mL, intra-assay CV: 2.50%, interassay CV: 3.23%), and P (analytical sensitivity: 0.1 ng/mL, intra-assay CV: 1.13%, interassay CV: 1.72%).

The statistical analyses were performed using SPSS for Windows (SPSS Inc., Zonguldak Karaelmas University, Zonguldak, Turkey) statistical package. The data were expressed as median (range). Mann-Whitney U and Kruskal-Wallis tests were used to compare nonparametric data. The correlation between endometrial thickness and E_2 was studied with Pearson correlation test. Type 1 error was set at 0.05. A sample size of at least 45 cycles in each group was required to detect a difference of 250 pmol/L in E_2 and a difference of two follicles on day of hCG administration between the two groups. This sample size is also sufficient to detect an odds ratio (OR) of 4 between these groups, with a α (type I error) set at 0.05, and 80% power.

RESULTS

One hundred nineteen cycles of ovulation induction were carried out in 46 patients. The median age, day 3 FSH, and E_2 levels were comparable among the letrozole and CC groups (Table 1). The median duration of infertility was significantly higher in the letrozole group (P=.01) (Table 1). In the letrozole group, infertility was due to male factor in 12 cases (57%), minimal–mild endometriosis in 3 cases (14%), and unexplained in the remaining 6 cases (29%). In the CC group, the respective figures were comparable and were 14 (56%), 3 (12%), and 8 (32%).

Four patients in the letrozole group were lost to follow-up. The remaining 21 patients in the letrozole group underwent 52 ovulation induction cycles. Patients were scheduled for timed intercourse in 25 cycles and IUI in 27 cycles. Twenty-five patients in the CC group underwent 67 ovulation induction cycles. Patients were scheduled for timed intercourse in 31 cycles and IUI in 36.

The ovulation induction data of the two groups are given in Table 2. The median number of follicles >15 mm in

TABLE 2

Ovulation induction outcome of the letrozole and CC groups.

Variable	Letrozole	CC	*P* value
No. of follicles >15 mm in diameter on the day of hCG	1 (0–4)	1 (0–5)	.06
Endometrial thickness the day of hCG (mm)	8 (5–12)	8 (4–13)	.67
E_2 level on the day of hCG (pg/mL)	191.5 (46–1,204)	476.0 (48–2,326)	.001
E_2 per follicle >15 mm in diameter on the day of hCG (pg/mL)	170.5 (46–949)	398.0 (48–1313)	.003
Pregnancy rate per cycle (%)	5/52 (10%)	8/67 (12%)	.9

Note: Pregnancy rate per cycle is expressed as N (%), all other values are median (range).

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diameter and endometrial thickness on the day of hCG administration were comparable among the two groups. In the CC group, the bilayer endometrial thicknesses on the day of hCG administration was >5 mm in 61 cycles; in the remaining 6 (9%) cycles it was <5 mm. None of these six cycles resulted in pregnancy. The bilayer endometrial thickness was >5 mm in all cycles in the letrozole group. Although there was a significant positive correlation between endometrial thickness and E_2 in the letrozole group ($r = 0.62$ and $P<.01$), no such significant correlation was noted in the CC group ($r = 0.20$ and $P>.05$).

The median E_2 level on the day of hCG administration was significantly lower in the letrozole group ($P=.001$) (Table 2). The median E_2 level per follicle >15 mm in diameter was significantly lower in the letrozole group ($P=.003$) (Table 2). Ovulation occurred in 81% (42/52) and 85% (57/67) of the cycles in letrozole and CC groups, respectively ($P=.71$). Five (9%) and eight (12%) patients conceived in the letrozole and CC groups, respectively ($P=.9$) (Table 2). Two (7.4%) and three (8.3%) patients conceived with IUI cotreatment in the letrozole and CC groups, respectively. Other than a single case of miscarriage in the CC group, the remaining 12 pregnancies resulted in healthy term delivery. No multifetal pregnancy or side effects were noted in the letrozole and the CC groups.

DISCUSSION

Letrozole (4, 4′-[1H-1, 2, 4-triazol-1-ylmethylene]-*bis*-benzonitrile) is a type II, third generation, cytochrome P-450 linked aromatase inhibitor that reversibly suppresses E biosynthesis. When administered in the early follicular phase, letrozole, by blocking E synthesis reduces the negative feedback effect of E on the hypothalamus or hypophysis. This results in an increased secretion of gonadotropins similar to the effect of CC. When used in the follicular phase of the cycling Bonnet monkeys, letrozole has been noted to increase serum gonadotropin, A levels, and stimulate follicular maturation (8). Letrozole was shown to increase LH and T levels in rats (9). In primates a stimulatory effect of androgens on follicular growth by amplification of FSH gene expression has been reported (10, 11). Letrozole may induce accumulation of ovarian A and thus increased expression of FSH receptors resulting in increased sensitivity of the developing follicles to FSH (10, 11). High oral bioavailability and relatively short half-life (45 hours) make letrozole a suitable agent for ovulation induction (12).

There is a paucity of data on the use of letrozole as an ovulation induction agent in anovulatory infertility (4) and as a part of empirical treatment (5, 13–15). Mitwally and Casper (4) have reported the use of letrozole in 12 patients with polycystic ovary syndrome (PCOS) and 10 patients with ovulatory infertility. Letrozole was given in a dose of 2.5 mg on days 3–7 of menses. In the PCOS group, ovulation occurred in nine patients (75%) and pregnancy was achieved in three (25%). In ovulatory patients, ovulation occurred in all cycles. The mean number of follicles measuring >15 mm in diameter on the day of hCG administration was 2.3 (range, 1–4). One pregnancy (10%) was reported.

Mitwally and Casper (16), in another study, evaluated the use of letrozole with exogenous FSH in 12 patients with unexplained infertility and a history of poor ovarian response to FSH in at least two previous cycles. Previous poor response was defined as less than three follicles 18 mm in diameter on the day of hCG administration (17). Letrozole was administered from days 3–7 at a dose of 2.5 mg/day and FSH treatment (50–225 IU/day) was started on days 5–7. Intrauterine insemination was performed in all cycles. Improved response to exogenous FSH stimulation with letrozole cotreatment was noted by the significantly lower FSH dose associated with significantly higher number of mature follicles. Three (21%) pregnancies were achieved. Healey et al. reported similar findings in 205 IUI cycles; addition of letrozole to FSH treatment decreased FSH requirement and increased the number of preovulatory follicles (13). Although endometrial thickness was decreased, no negative effect on pregnancy rates (PR) was noted.

In this study we compared letrozole with CC as the first-line therapy for ovulation induction in patients with borderline male factor infertility, early-stage endometriosis, and unexplained infertility. Being not a blinded study and quasi-randomization are weaknesses of our study. Because our study was a pilot study and the sample size limited, the duration of infertility was significantly higher in the letrozole group. Despite this significant difference PRs of two groups were comparable. All ovulation induction outcome measures, excluding serum E_2 level and E_2 level per follicle >15 mm in diameter, were comparable among the CC and letrozole groups. Pregnancy rates were also comparable.

Although median endometrial thickness was comparable among the CC and letrozole groups, it was less than 5 mm in six CC cycles; however, in none of the letrozole cycles it was less than 5 mm. Although, our sample size is limited, a lack of detrimental effect on endometrial thickness may be a favorable finding with letrozole treatment. There are limited data on the effect of letrozole on endometrium. Cortinez et al. (14), in letrozole-treated patients, reported normal morphology of endometrium and full expression of pinopodes during the implantation window. Mitwally and Casper (4) reported significantly higher endometrial thickness on the day of the hCG administration with letrozole compared with CC, despite significantly lower E_2 levels in the former. On the other hand, no significant difference was noted in other studies (14, 17), including an animal study (18).

Due to significantly lower E_2 levels, letrozole may be considered for empirical ovulation induction in infertile patients with E-dependant neoplasms. We conclude that letrozole is as effective as CC and may be an alternative to CC in ovulation induction protocols for both IUI and timed intercourse.

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