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Original Article

Comparison of the success rate of letrozole and clomiphene citrate in women undergoing intrauterine insemination

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Abstract

BACKGROUND: This study was conducted to compare the success rate of daily administration of aromatase inhibitor letrozole at a dose of 5 mg when administrating clomiphene citrate (CC) 100 mg daily in women undergoing superovulation and IUI.

METHODS: This prospective randomized trial was done in Research and Clinical Center for Infertility (Shahid Sadoughi University), Yazd, Iran. Ninety-five patients with unexplained and mild male factor infertility were studied. Using a computer-generated random table, the patients were randomized into two groups, which were treated with 5 mg of letrozole daily (42 patients, 42 cycles) or 100 mg of CC daily (53 patients, 53 cycles). The data were analyzed using Student's t-test and chi square test.

RESULTS: The mean age and duration of infertility in both groups were similar. There was a significant difference between the two groups in the total numbers of follicles during stimulation (5.45 ± 4.2 in CC group vs. 3.07 ± 2.1 in letrozole group) (P = 0.01). No significant difference in the endometrial thickness was found between the two groups (letrozole group = 6.9 ± 2.2, CC group = 7.8 ± 1.8). The mean levels of LH and FSH in both groups were similar. P value of difference in hormone levels between two groups were 0.33 and 0.47, respectively, but there was a significant difference in mean E2 levels between the two groups (241.28 ± 167.537 in letrozole group vs. 867.34 ± 296.689 in CC group) (P = 0.018). The mean number of gonadotropin ampules used in both groups was the same. Pregnancy rate per cycle was 9.5% in the letrozole group and 5.7% in the CC group (P = 0.6). Two out of the three pregnancies in the CC group (66.6%) and one out of the four pregnancies in the letrozole group resulted in a miscarriage (25%). One twin pregnancy (33%) occurred in the letrozole group and none in the CC group. Ovarian hyperstimulation syndrome (OHSS) did not occur in either of the two groups.

CONCLUSIONS: In IUI, superovulation with clomiphene citrate and letrozole was associated with similar pregnancy rates, but the miscarriage rate was higher with clomiphene citrate.

KEY WORDS: IUI, letrozole, clomiphene citrate, superovulation.

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The principal medications available for ovarian stimulation are oral antiestrogen, clomiphene citrate (CC), and injectable gonadotropins and aromatase inhibitor [1]. CC has a long half-life and accumulates in the body [2]. In anovulatory women, the use of CC is widely accepted as the first line therapy because of its low cost and easy administration [3, 13]. Its use is associated with a high ovulation rate of 60%-80%, but with a lower pregnancy rate of about 50% [3] and some side effects [1]. This may be due to a detrimental effect on the endometrium (an estrogen responsive site) and on the quality of cervical mucus [2]. The

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endometrium is believed to be one of the most important targets for the antiestrogenic effect of CC and may explain a large part of its low pregnancy rate and high miscarriage rate. Successful implantation requires a receptive endometrium, with synchronous development of glands and stroma [4, 5]. In one study, CC was found to have a deleterious effect on the endometrium, demonstrated by a reduction in glandular density and an increase in the number of vacuolated cells [6]. In addition, Gonen et al (1990) demonstrated a reduction in endometrial thickness, below the level thought to be needed to sustain implantation, in up to 30% of women receiving CC for ovulation induction or for unexplained infertility [7]. Recently, it was suggested that letrozole, a specific reversible, nonsteroidal aromatase inhibitor that suppresses estrogen biosynthesis [8], could successfully replace CC in superovulation treatment of patients with unexplained infertility or polycystic ovarian syndrome and in poor responders [9]. The new third generation aromatase inhibitors agents commercially available include two nonsteroidal preparations, anastrozole and letrozole and a steroidal agent, exemestane [10,11]. Letrozole has a short half-life (around 2 days) and it clears rapidly from the body [12]. This drug is a potent and highly specific nonsteroidal aromatase inhibitor that initially was approved for use in postmenopausal women with breast cancer to suppress estrogen production [13,14]. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a blockade of androgens conversion into estrogens with subsequent increase in intraovarian androgens [15]. Administering letrozole early in the follicular phase induces ovulation by releasing the hypothalamus or pituitary from estrogen negative feedback on GnRH and gonadotropin secretion, leading to an increase in gonadotropin production which would stimulate ovarian follicular development [12] but unlike clomiphene citrate, does not lead to estrogen receptor depletion [16]. Letrozole increases intraovarian androgen levels and may synergize with the central effects of decreased estrogen to enhance ovarian response to gonadotropin stimulation [1]. The combined use of aromatase inhibitors and gonadotropin injection was associated with improved ovarian response [17].

The purpose of the present study was to compare the effects of administrating 5 mg of letrozole daily in women undergoing IUI with these effects when administrating 100 mg of CC.

Methods

In total, 95 patients with unexplained and mild male factor infertility were studied at Yazd Research and Clinical Center for Infertility. Inclusion criteria were age younger than 40 years, infertility of more than 1 year in duration, patent fallopian tubes on hysterosalpingogram or laparoscopy and the presence of at least 10 million rapidly motile sperm/ml (mild male factor) [16]. Patients were randomized using a computer-generated random table into two groups which were treated with 5 mg of letrozole daily (42 patients, 42 cycles) or 100 mg of CC daily (53 patients, 53 cycles). In the letrozole group, the patients were treated with letrozole (Femara; Novartis pharmaceuticals, Dorval, Quebec, Canada) 5 mg/day on days 3-7 of the menstrual cycle and FSH (Gonal-F, Serono, Ontario, Canada or puregon; organon) (150 IU/day) on day 8, while patients in CC group were treated with clomiphene citrate 100 mg/day on days 5-9 of the menstrual cycle and FSH (150 IU/day) from day 8. Ultrasound examination was started on day 12 and the following days when the diameter of the dominant follicle reached 18 mm, HCG (10,000 IU) was administrated for triggering ovulation followed by IUI after 34-36 hours. We evaluated the total number and size of the follicles, endometrial thickness and type, the number of gonadotropin ampules, mean LH, FSH and E2 levels, pregnancy rate (chemical and clinical) and miscarriage rate. Data were analyzed using Student's t-test and chi-square test. Results were expressed as mean and standard deviation. P values below 0.05 were considered as statistically significant.

Results

Our results show that the causes of infertility, mean age and duration of infertility in both groups of patients were similar (table 1). The total numbers of follicles in the letrozole group were lower than those in the clomiphene citrate group. There was no significant difference in endometrial thickness between the two groups (6.9 ± 2.2 mm in the letrozole group, 7.8 ± 1.8 mm in the CC group). The mean numbers of gonadotropin ampules used in the two groups were the same. (P = 0.19) (table 2).The mean levels of LH and FSH in the groups were similar. (P values for the difference in hormone levels between the two groups were 0.33 and 0.47, respectively). There was a significant difference in mean E2 levels between the groups (241.28 ± 167.537 in letrozole group vs. 867.34 ± 296.689 in CC group) (P = 0.018) (table 2). The pregnancy rate per cycle was 9.5% in the letrozole group and 5.7% in the CC group (P = 0.6). One out of the four pregnancies in the letrozole group (25%) and two out of the three pregnancies in the CC group (66.6%) resulted in miscarriage (table 3). OHSS did not occur in either of the two groups. One twin pregnancy (33%) occurred in the letrozole group and none in the CC group.

Table 1. Characteristics of patients undergoing superovulation with letrozole or clomiphene citrate (CC).

Characters	Letrozole N = 42	CC N = 53	P value
Mean (± SD) age of women, years	29 ± 2.9	25.7 ± 3.8	NS*
Mean (± SD) age of men, years	31.88 ± 4.3	30.66 ± 4.01	NS
Mean (± SD) duration of infertility, years	5.95 ± 2.4	5.23 ± 2.5	NS
Causes of infertility			
Male factor (%)	23.8	34	NS
Unexplained (%)	76.2	66	NS

*NS = Not Significant

Table 2. Superovulation with letrozole or with clomiphene citrate (CC).

	Letrozole N = 42	CC N = 53	P value
Mean (± SD) number of total follicles	3.07 ± 2.1	5.45 ± 4.2	0.01
Mean (± SD) endometrial thickness (mm)	6.9 ± 2.2	7.8 ± 1.8	NS
Mean (± SD) of LH (IU/L)	8.07 ± 10.96	8.24 ± 7.8	NS
Mean (± SD) of FSH (IU/L)	6.39 ± 3.3	7.3 ± 4.4	NS
Mean (± SD) of E2 (pg/ml)	241.28 ± 167.537	867.34 ± 296.689	0.018
Mean (± SD) number of gonadotropin ampule	6.1 ± 2.4	7.7 ± 3.4	NS

*NS= Not Significant

Table 3. Outcome of letrozole or clomiphene citrate in women undergoing IUI.

	Letrozole N = 42	CC N = 53	P value
Number of pregnancies	4 (9.5%)	3 (5.7%)	NS
Ongoing pregnancies	3	1	NS
Miscarriage	1	2	NS

*NS= Not Significant

Discussion

Clomiphene citrate is the most commonly prescribed agent for ovulation induction. Unfortunately, despite the high rates of ovulation, pregnancy rates per cycle remain relatively low. An antiestrogenic effect of clomiphene on the endometrium has been postulated. Mitwally and Casper (2001) have shown that the use of CC may be complicated owing to the

antiestrogenic effects on endometrial development. For these reasons, a simple, inexpensive and safe alternative to CC for use in normally ovulatory woman is required [18]. The addition of IUI to Controlled Ovarian Hyperstimulation (COH) by CC or gonadotropins was shown to be significantly more effective than COH alone [19-21]. Several authors found combined COH and IUI treatment to be very effective in unexplained and mild male infertility [22-24]. Stephanie et al (2002) compared the effect of clomiphene citrate and letrozole on normal ovulatory women; profiles of both LH and FSH were similar in natural and medicated cycles with letrozole and CC, but E2 level was more than two times higher in clomiphene-treated cycles [25]. Despite significantly lower E2 levels in letrozole-treated women, endometrial development was unaffected in this study. In a selected population of women with endometrium (mean thickness of 5mm) after clomiphene treatment, letrozole treatment in the early follicular phase resulted in a significant increase in midcycle endometrial thickness (mean thickness of 9 mm) [18]. These results were similar to our study. A larger randomized trial is required to fully assess the impact of letrozole on endometrial development. Al-Fozan et al [26], compared the effect of CC and letrozole in women undergoing superovulation. There was no difference in pregnancy rates or endometrial thickness between the letrozole and the CC groups. Of interest, the miscarriage rate was higher in the CC group [26,27,28]. This may have been due to the different mechanisms of action of letrozole and CC [26]. In our study, there was no difference in pregnancy rates or in endometrial thickness between the groups. Mohamed F et al (2005) showed the effect of an aromatase inhibitor for ovarian stimulation on pregnancy outcome; they found CC treatment to be consistently associated with development of more ovarian follicles than with aromatase inhibitor and the lowest multiple gestation rate was associated with letrozole treatment [29]. In our study, the results of follicles development were the same, but multiple-gestation rate was higher with letrozole treatment. More studies on larger numbers of multiple-gestation cases with letrozole are needed to confirm these findings. Our results showed significantly lower estradiol concentrations in the letrozole group than in the CC group and more follicles were observed in cycles stimulated with 100 mg CC from day 3 to 7 of the cycle than in the letrozole group. These results are similar to those of Fatemi's research (2003) [30].

The estrogen levels in women on aromatase inhibitors were found to be 2-3 times lower than those reported in CC cycles, however, endometrial thickness was greater in the aromatase inhibitor cycles [2]. In our study, estrogen levels were higher in the CC group, but there was no difference in the endometrial thickness between the two groups. Letrozole, at doses of 1-5 mg/day, inhibits aromatase activity by 97%-99% [11]. In all studies conducted so far, the aromatase inhibitor letrozole was administered as a 5-day regimen, usually from day 3 to 7 of the menstrual cycle, at a dose of 2.5-7.5 mg/day [10,31]. Even in one study [10] the new approach of a single-dose regimen of an aromatase inhibitor for ovarian stimulation seems to be as effective as the previously reported 5-day regimen. In the present study, letrozole was administrated at a dose of 5 mg/day from day 5 to 9 of the menstrual cycle. It was shown that CC is associated with increased risk of severe ovarian hyperstimulation syndrome and high multiple pregnancies [1]. In the present study, OHSS did not occur in either of the two groups. Mitwally and Casper (2004) proposed that aromatase inhibitors would replace CC in the future as the new primary treatment for ovulation induction in PCO patients [11]. Letrozole can be used for ovulation induction or ovarian stimulation with higher pregnancy rates compared with CC [18].

In summary, the results of this preliminary study suggest that the aromatase inhibitor, letrozole, may be used as an alternative new first-line treatment for ovulation induction in ovulatory infertile patients. This research was conducted before warnings of letrozole side effects on the internet.

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