The Journal of Obstetrics and Gynecology of India
https://doi.org/10.1007/s13224-024-01956-y

ORIGINAL ARTICLE

Comparison of Administration of Letrozole 20 mg Single Dose Versus 25 mg in Divided Doses to Stimulate Ovulation in IUI Cycles

Elham Hashemi[1] · **Zahra Heidar**[2]

Received: 6 November 2023 / Accepted: 13 January 2024

Abstract

Background Although letrozole has been used for ovulation disorders in intra-uterine insemination (IUI) for a long time, the dose and method used have not been determined.

Methods This randomized clinical trial was conducted in 200 eligible infertile women who were candidates for IUI. They were randomly divided into two groups: in the first group, a single dose of 20 mg of letrozole tablet prescribed on the third day of the cycle, and in the second group, on the third to the seventh days of the cycle, 5 mg of letrozole tablets were prescribed every day (in total, 25 mg in divided doses). The patients underwent transvaginal ultrasound on days 9–11 of the cycle, and the size of the follicles and the thickness of the endometrium were examined and if the patient's follicles were suitable, IUI was performed.

Findings 137 patients (69%) had one or more follicles higher than 14 mm. The mean (SD) diameter of the largest follicle and endometrial thickness were 15.0 ± 2.9 mm and 5.5 ± 1.4 mm, respectively, which were not significantly different between the two groups ($P > 0.05$). Pregnancy occurred in 62 patients (31%) and in 10 patients (5%) abortion occurred in the first trimester with no significant difference between the two groups ($P > 0.05$).

Conclusion Prescribing letrozole 20 mg as a single dose on the third day of the cycle to stimulate ovulation in IUI cycles has comparable effects with 5 divided doses of 5 mg on the third to seventh days of the cycle.

Keywords Infertility · Intra-uterine insemination (IUI) · Letrozole · Ovulation stimulation

Introduction

Ovulation induction is one of the methods of treating infertility caused by anovulatory infertility [1] and the most common drugs used in the treatment of ovulation disorders are clomiphene citrate and letrozole [2]. Aromatase inhibitors such as letrozole, which are widely used in the treatment of breast cancer patients, have been introduced as an alternative to clomiphene in ovulation induction [3]. Regarding the pregnancy rate, the results are different and in some studies, it is higher in the letrozole group and in others, the same pregnancy rate has been reported [2, 4].

Although letrozole side effects are minor and have not been reported in short-term use and in young women [5–7], the ideal dose and duration of use are still not well known. In a randomized clinical trial, doses of 2.5, 5, and 7 mg per day were administered from day 3 to 7 of the cycle (5 days), and the effect of the 5 mg daily dose was greater than 2.5 mg and similar to the 7 mg dose.The effect of all three doses was similar in a study, while in another study, the administration of a dose of 2.5 mg for ten days with a dose of 5 mg for five days in people with polycystic ovary syndrome (PCOS) resistant to treatment has led to more pregnancies [4].

In a more recent study, the use of a high dose of letrozole of 20 mg per day for three cycles compared to the administration of 5 mg on days 3–7 caused similar estradiol levels, endometrial thickness, and pregnancy rates, with the difference that in the regimen 20 mg, the therapeutic effect remains for about five days and until the 13th day, its effect is

Dr. Elham Hashemi: Obstetrics and Gynecology Specialist; Dr. Zahra Heidar: Associate Professor of Obstetrics and Gynecology.

✉ Elham Hashemi
helham260@gmail.com

[1] Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Present Address: Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Published online: 16 February 2024

completely removed, and it cannot cause a teratogenic effect at the time of implantation [5, 6]. In some studies, letrozole was used along with FSH in ART cycles in poor responders and acceptable results were obtained [5, 6]. Although letrozole has been used as an ovulation stimulation drug for more than a decade, and the results of all studies have shown that it has a comparable effect if not more effective than clomiphene, but due to the fear of its teratogenic effects, its use is still widespread like clomiphene. It has not been used and its use in Europe and America as an ovulation stimulation drug is not allowed and it is allowed only for conducting research and obtaining consent. In 2005, the American society for reproductive medicine (ASRM) published the results of a study showing that locomotor malformations and cardiac abnormalities were more common in pregnancies with letrozole. Of course, there are many problems in that study, such as the fact that the case and control groups were not the same in terms of age and underlying diseases, the average age of the mother was higher in the treatment group, and we know that the age of the mother itself has an effective role in the prevalence of congenital anomalies. Also, the rate of multiple pregnancies was higher in the treatment group (in multiple pregnancies, the prevalence of some anomalies increases). On the other hand, the control group was selected from patients admitted to the low-risk ward. All these differences can distort the results of the study [4, 8]. In all subsequent studies, the overall prevalence of anomalies did not increase in the letrozole group, and comparing pregnancies resulting from letrozole use and without treatment, no difference was observed in the amount of fetal disorders [5, 6, 9].

Therefore, it can be said that despite all the beneficial effects and the positive effect of letrozole on the pregnancy rate due to the lack of FDA approval, the use of this drug is better only in special cases and with the consent of the patient. Obviously, a lot of research is being done on the safety of this drug and determining the best dosage around the world. Considering the importance of infertility and considering that the studies conducted in this field did not have definitive results and the number of them, the aim of this study is to investigate and compare the administration of letrozole tablets in stimulation of the ovulation cycle in two ways: a single dose of 20 mg on the third day of the cycle and 25 mg in divided doses (5 mg daily from the third to the seventh day of the cycle).

Methods

This randomized, single-blind clinical trial was conducted in 2022 in infertile women referred to the infertility department of Mahdieh Hospital in Tehran, who were candidates for ovulation stimulation treatment with IUI. Inclusion criteria include being 20–40 years old, having a history of infertility for at least one year, the absence of underlying disease such as abnormality of thyroid stimulating hormone and prolactin, spermogram within the acceptable range for IUI, having at least one open fallopian tube and consent to participation in the study. Exclusion criteria include history of allergy to letrozole and other aromatase inhibitor drugs, history of allergy to cabergoline and other ergot derivatives, history of pelvic surgery, and presence of any infertility factor other than lack of ovulation.

The sample size was estimated 100 patients in each group based on 5% type 1 error level, 90% power, using the index of the number of days needed to reach follicular maturity in a similar study [10], and 5% shedding. Sampling was done in a non-random and easy way (available sample) and the classification of the samples to be assigned to treatment groups was done in a block random manner and the individual randomization unit is considered. RAS statistical software was used as a tool for block randomization and determining the sequence of blocks. Also, the sealed cover letter was used for allocation concealment. The capacity of the blocks was considered to be 4 and then all the possible permutations for this block were written, which were defined as follows: (1: ABAB), (2: AABB), (3: BBAA), (4: BABA), (5: ABBA) and (6: BAAB). By means of statistical software, we randomly selected one of the numbers of the permutations and considered the block corresponding to it. For example, if the first random selection of block was 5, the first patient would receive treatment A, the second and third patients would receive treatment B, and the fourth patient would receive treatment A. To reach a sample size of 100 in each group, we continued this process 25 times. After selecting all the blocks, we randomly assigned index A and B to one of the treatment groups. Thus, 100 patients in each group were included in the study. All patients completed the study.

At first, the purpose of the research and the importance of regular drug use were explained to the mothers and informed consent was obtained. In the first visit, demographic information including age, education and occupation was recorded. Then the patients were randomly divided into two groups. In the first group, a single dose of letrozole 20 mg was prescribed on the third day of the cycle. In the second group, from the third day of the cycle, for five days, 5 mg of letrozole tablets (two 2.5 mg tablets at once—a total of 25 mg divided) were prescribed. Then, the patients in both groups underwent transvaginal ultrasound on days 9 to 11 of the cycle, and the size of the follicles and the thickness of the endometrium were examined. If no follicle above 14 mm was seen, one HMG ampoule was prescribed a day and the patient underwent ultrasound examination two days later. The number of observed follicles and the diameter of the largest follicle were recorded. In the case of seeing a follicle above 14 mm, HCG was injected in the follicle size of 18–19 mm and IUI was performed 36 h after that.

Table 1 Comparison of patient characteristics between two groups

		Letrozole group 25 mg divided (100 persons)	Letrozole group 20 mg single dose (100 persons)	*P* value
Age, year		29 ± 5	31 ± 5	0.139*
Education	Under diploma	18 (18%)	15 (15%)	0.568**
	Diploma or uppers	82 (82%)	85 (85%)	
Occupation	housewives	86 (86%)	90 (90%)	0.384**
	employed	14 (14%)	10 (10%)	

*Independent sample t test, ** Chi square test

The number of follicles above 14 mm on days 9–11 of the cycle and the diameter of the largest of them, the amount of HMG consumed, the incidence of pregnancy and abortion were recorded. The patients were instructed to go to the hospital immediately in case of any emergency problem such as abdominal pain, nausea, vomiting, etc. Drug side effects were also recorded. The doctor who performed the ultrasound and the data analyzing person did not know about the patient group. At the end, all variables and outcomes were compared between the two groups.

SPSS 25 statistical software was used for data entry and analysis. Qualitative variables were described using frequency and percentage, and quantitative variables were described using mean and standard deviation. In order to analyze the data, chi-square statistical tests and independent t-test were used. $P < 0.05$ was considered as a significant level.

Results

Characteristics of Patients

The range and mean (standard deviation, SD) of the patients' ages were 20–39 years and 30 ± 5 years, respectively. 167 patients (83%) had diploma or higher education. Also, 176 patients (88%) were housewives and 24 patients (12%) were employed. There was no significant difference between the two groups in terms of age, education and occupation (Table 1).

The Number of Follicles Above 14 mm on Days 9–11 of the Cycle

A total of 63 patients (31%) had no follicles greater than 14 mm on days 9–11 of the cycle. 67 people (34%) had one follicle, 50 people (25%) had two follicles and 20 people (10%) had three or more follicles above 14 mm on days 9–11 of the cycle (Fig. 1). The number of follicles had no statistically significant difference between the two groups (Table 2, $P = 0.958$).

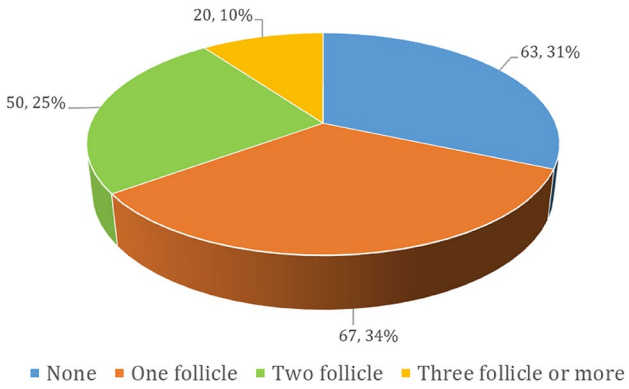

Fig. 1 The number of follicles greater than 14 mm on days 9–11 of the cycle in all patients

Table 2 Comparison of the number of follicles larger than 14 mm on days 9–11 of the cycle between the two groups

	Letrozole group 25 mg divided (100 persons)	Letrozole group 20 mg single dose (100 persons)	*P* value*
None	32 (32%)	31 (31%)	0.958
One	33 (33%)	34 (34%)	
Two	26 (26%)	24 (24%)	
Three or more	9 (9%)	11 (11%)	

*Chi square test

The Diameter of the Largest Follicle on Days 9–11 of the Cycle

The range and mean (SD) of the diameter of the largest follicle of the patients on days 9–11 of the cycle were 9–21 mm and 15.0 ± 2.9 mm, respectively, which did not have a significant difference between the two groups of letrozole single dose 20 mg and letrozole 25 mg divided (15.0 ± 2.8 mm and 15.0 ± 3.1 mm, respectively, $P = 0.817$).

Endometrial Thickness on Days 9–11 of the Cycle

The range and mean (SD) of the endometrial thickness of the patients on days 9–11 of the cycle were 3–10 mm and

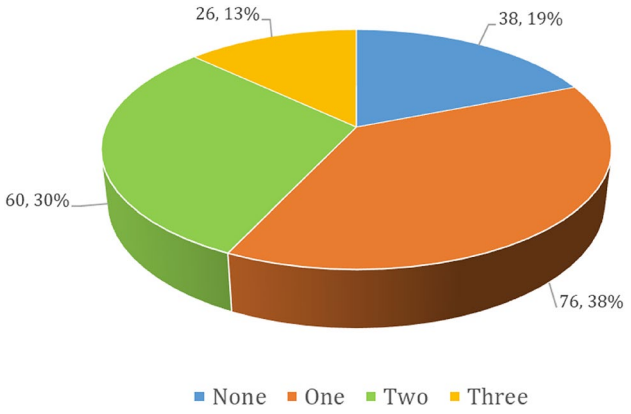

Fig. 2 Number of HMG ampoules used in all patients

Table 3 Comparison of the number of HMG ampoules consumed between the two groups

	Letrozole group 25 mg divided (100 persons)	Letrozole group 20 mg single dose (100 persons)	*P* value*
None	16 (16%)	22 (22%)	0.499
One	36 (36%)	40 (40%)	
Two	33 (33%)	27 (27%)	
Three	15 (15%)	11 (11%)	

*Chi square test

5.5 ± 1.4 mm, respectively, which did not have a significant difference between the two groups of letrozole single dose 20 mg and letrozole 25 mg divided (5.5 ± 1.4 mm and 5.6 ± 1.3 mm, respectively, $P = 0.602$).

The Number of HMG Ampoules Consumed

A total of 38 patients (19%) did not receive any HMG ampoules. One ampoule was used in 76 patients (38%), two ampoules in 60 patients (30%) and three ampoules in 26 patients (13%) (Fig. 2). There was no significant difference between the two groups in terms of the number of HMG ampoules consumed (Table 3, $P = 0.499$).

Drug Side Effects

In total, 3 patients (1.5%) had drug complications, all three cases were ovarian cysts. There were two cases (1%) in the letrozole 25 mg divided group and one case (0.5%) in the letrozole single dose 20 mg group, which had no significant difference between the two groups ($P = 0.516$).

First trimester Pregnancy and Abortion

Pregnancy occurred in 62 patients (31%), 29 cases (29%) in the divided letrozole 25 mg group and 33 cases (33%) in the single dose letrozole 20 mg group, which was not significantly different between the two groups ($P = 0.541$). Also, 10 patients (5%) had first trimester abortion, which was 5 cases (5%) in each group ($P = 1.000$).

Discussion

The findings of the present study showed that, on days 9–11 of the cycle, 137 patients (69%) had at least one follicles larger than 14 mm. The mean (SD) diameter of the largest follicle was 15.0 ± 2.9 mm and the mean (SD) thickness of the endometrium was 5.5 ± 1.4 mm. There was no significant difference between the two groups of single-dose letrozole and divided letrozole in terms of the number of follicles greater than 14 mm, diameter of the largest follicle, and endometrial thickness. Only 3 patients (1.5%) had a drug complication, and all three cases were ovarian cysts. Pregnancy occurred in 62 patients (31%), of which 29 cases (29%) were in the letrozole 25 mg divided group and 33 cases (33%) were in the letrozole 20 mg single dose group. In 10 patients (5%) abortion occurred in the first trimester. There was no significant difference between the two groups in terms of drug side effects, pregnancy rate and first trimester abortion. In total, our study showed that the administration of letrozole 20 mg as a single dose on the third day of the cycle or divided into 5 doses of 5 mg on the third to seventh days of the cycle does not make a significant difference in ovarian response.

Although letrozole has been used for years to stimulate ovulation in infertility, especially IUI, the doses used are still in question. In most studies, a dose of 5 mg per day for 5 days from the third to the seventh day of the cycle has been used. But in some other studies, doses of 2.5 and 7.5 mg have also been used. Although several articles have compared letrozole and other treatments such as clomiphene citrate and gonadotropins, few studies have investigated and compared different doses of letrozole. In a 2006 clinical trial, Al-Fadhli et al. examined the effects of letrozole at doses of 2.5 and 5 mg daily in 72 women undergoing IUI and reported that, compared to the 2.5 mg dose, in the patients receiving the 5 mg dose, the number of follicles was significantly higher, but the thickness of the endometrium was not significantly different between the two groups. Also, the pregnancy rate was significantly higher in patients who received a dose of 5 mg compared to patients who received a dose of 2.5 mg (26.3% vs. 5.9%). Therefore, they have reported a dose of 5 mg for 5 days to induce ovulation as more useful [11]. In a 2007

clinical trial, Badawy et al. examined three doses of letrozole 2.5, 5, and 7.5 mg in induction of ovulation in 179 patients with unexplained infertility and reported that the total number of follicles, follicles higher than 14 mm and follicles higher than 18 mm on the day of hCG injection were significantly higher in the 7.5 mg group. However, the rate of pregnancy and abortion was not significantly different between the three groups. Finally, it has been stated that it seems that higher doses of letrozole have no effect on the pregnancy rate compared to lower doses [12]. In a 2008 clinical trial, Noriega-Portella et al. compared the effect of combination therapy of letrozole 2.5 mg and letrozole 5 mg with recombinant FSH in 110 women undergoing IUI and treatment with gonadotropins and reported that women in the group recombinant FSH plus letrozole 5 mg required a lower dose of recombinant FSH compared to the group of recombinant FSH alone or combined with 2.5 mg letrozole. In all follicular phases, the thickness of the endometrium in the letrozole groups was lower than the recombinant FSH group. But on the day of hCG administration, the thickness of the endometrium was not significantly different between the groups. The pregnancy rate was not significantly different between the groups. Finally, it has been stated that in terms of cost benefit, it seems that letrozole with a dose of 5 mg is more effective than 2.5 mg without having an effect on the rate of pregnancy or the outcome of patients. [13]. In a 2011 retrospective study, Pritts et al. reviewed more than 900 cycles of high-dose letrozole (12.5 mg/day) and reported that these high doses were associated with higher follicle counts and growth. The follicles were accompanied, but it did not cause a significant increase in the thickness of the endometrium. The average number of follicles with doses of 10 and 12.5 mg/day was equal to 2.2, with a dose of 5 mg/per day equal to 1.6, and with a dose of 7.5 mg/day equal to 1.7. The thickness of the endometrium was higher up to 0.27 mm with a dose of 12.5 mg/day. Finally, it has been stated that high doses of letrozole can be effective in women who do not respond well to lower doses. However, more studies are needed in this field [14]. Finally, in a 2013 review, Kar et al., by reviewing the published articles on the use of letrozole in different cases, reported that higher doses of letrozole increased the ovarian response and increased the number of follicles, but there was no significant change in endometrial thickness compared to lower doses [10]. Despite an extensive search of the scientific literature, more recent studies comparing different doses of letrozole were not available. The results of our study showed that a single dose of 20 mg of letrozole on the third day of the cycle has similar effects to the usual method of letrozole administration. Therefore, considering the similar effects of these two methods and that the single dose method may be more accepted by the patient and it is even more acceptable for patients in terms of mental state, it is possible to recommend the use of this method in patients undergoing IUI. However, more extensive studies are needed in this field.

Conclusion

The findings of our study showed that the administration of letrozole 20 mg as a single dose on the third day of the cycle or divided into 5 doses of 5 mg on the third to seventh days of the cycle to stimulate ovulation in IUI cycles has no significant difference in ovarian response, endometrium thickness, the amount of HMG ampoule used, drug side effects, the rate of pregnancy and abortion. Therefore, it seems that the single dose administration method can be used for this purpose.

Declarations

Conflict of interest None.

Ethical standard In this study, all provisions of the Declaration of Helsinki were observed. Participation in the study was optional, and written consent was obtained from all patients upon entering the study. This study has a code of ethics from the ethics committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.MSP.REC.1401.375 and is registered on the Iranian clinical trials website with the code IRCT20220412054511N1.

References

1. Pavone ME, Bulun SE. The use of aromatase inhibitors for ovulation induction and superovulation. J Clin Endocrinol Metab. 2013;98(5):1838–44.
2. Kamath MS, George K. Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. Reprod Biol Endocrinol. 2011;9(1):86.
3. Ratts VS, Pauls RN, Pinto AB, et al. Risk of multiple gestation after ovulation induction in polycystic ovary syndrome. J Reprod Med. 2007;52(10):896–900.
4. Fouda UM, Sayed AM. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized controlled trial. Reprod Biol Endocrinol. 2011;9(1):84.
5. Sel G. Ovulation Induction. Practical Guide to Oral Exams in Obstetrics and Gynecology. Cham: Springer International Publishing; 2020, p. 269–73.
6. Kim SD, Jee BC. Ovulation induction: an up-to-date knowledge. Korean J Obstet Gynecol. 2009;52(7):691–9.
7. Bedaiwy MA, Abdelaleem MA, Hussein M, et al. Hormonal, follicular and endometrial dynamics in letrozole-treated versus natural cycles in patients undergoing controlled ovarian stimulation. Reprod Biol Endocrinol. 2011;9(1):83.
8. van Santbrink EJ, Eijkemans MJ, Laven JS, Fauser BC. Patient-tailored conventional ovulation induction algorithms in anovulatory infertility. Trends Endocrinol Metab. 2005;16(8):381–9.

9. Gill SK, Moretti M, Koren G. Is the use of letrozole to induce ovulation teratogenic? Can Fam Physician. 2008;54(3):353–4.
10. Kar S. Current evidence supporting "letrozole" for ovulation induction. J Hum Reprod Sci. 2013;6(2):93.
11. Al-Fadhli R, Sylvestre C, Buckett W, et al. A randomized trial of superovulation with two different doses of letrozole. Fertil Steril. 2006;85(1):161–4.
12. Badawy A, Metwally M, Fawzy M. Randomized controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reprod Biomed Online. 2007;14(5):559–62.
13. Noriega-Portella L, Noriega-Hoces L, Delgado A, et al. Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril. 2008;90(5):1818–25.
14. Pritts EA, Yuen AK, Sharma S, et al. The use of high dose letrozole in ovulation induction and controlled ovarian hyperstimulation. ISRN Obstetr Gynecol. 2011;2011:1–4.