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Original Research Article

Effect of letrozole 2.5 mg or 5.0 mg for ovulation induction in intrauterine insemination in case of unexplained infertility: a randomized controlled trial

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ABSTRACT

Background: Aim was to compare effects of letrozole 2.5 mg or 5.0 mg for ovulation induction in patients with unexplained Infertility.
Methods: A randomized controlled trial. 60 patients attending infertility clinic were randomly allocated into two groups-Group A received letrozole 2.5 mg and Group B received letrozole 5 mg orally for 5 days from 3rd day of cycle. The patients also received inj FSH 75 IU i/m on day 7 and 9 of the cycle and underwent follicular study on day 11, 13, 15. When the dominant follicle size reached 18 mm ovulation triggered with Inj hCG 5000 IU IM and Intrauterine insemination was done 24-36 hours later. Pregnancy rates were calculated. Results were analysed by statistical software.
Results: Better ovulation rates were seen in patients receiving 5 mg letrozole. No difference in the pregnancy rates was found between the two groups. No multiple pregnancies and ovarian hyperstimulation seen.
Conclusions: It appears that 5 mg daily for 5 days is a preferable letrozole dose for superovulation.

Keywords: Intrauterine insemination, Letrozole, Unexplained infertility

INTRODUCTION

Unexplained infertility represents up to 30% of all cases of infertility. It is a diagnosis of exclusion, where no cause for infertility may be identified in the couple's investigation, be it anovulation, fallopian tube blockage, or severe male factor.[1] In unexplained infertility, treatments like ovarian stimulation (O.S.), intrauterine insemination (IUI) without or with O.S. (OS-IUI), and IVF are one-cycle interventions that do not target a specific cause of infertility but rather increase the chance of pregnancy by increasing the number of oocytes that can be fertilized in one cycle and bringing the gametes closer. Controlled ovarian stimulation (C.O.S.) combined with intrauterine insemination (IUI) is a common infertility treatment as a low-cost, less-invasive alternative to in vitro fertilization (IVF) and was approved as a first-line treatment option for unexplained infertility.[2]

Clomiphene citrate (CC) has been the most widely used drug for the treatment of infertility since its introduction into clinical practice in the 1960s. It is known that

clomiphene citrate results in an ovulation rate of 60-85% but a conception rate of only about 20%.[3] Side effects of the drug can be psychologically difficult to endure (hot flashes and mood swings) and detrimental to fertility (impaired endometrial development and abnormal cervical secretions.[4] Gonadotropin therapy has more risks and is more expensive than oral ovulation induction agents and should therefore only be used by clinicians having the requisite training and experience.[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. As a result, F.S.H. secretion increases, stimulating the development of ovarian follicles.[6] They have no antiestrogenic effect on the endometrium, an advantage for keeping the endometrium in optimal condition to maintain a pregnancy. Therefore, A.I.s constitute an excellent alternative to clomiphene citrate treatment as an ovulation inductor for the treatment of infertility, particularly in assisted reproduction programs. The ideal daily dose of letrozole remains unknown.[6,7]

There are very few studies in women with unexplained infertility and PCOS patients in which increasing the letrozole dose resulted in more mature follicles. Based on the results of these studies, increasing the quantity of letrozole could increase the number of mature follicles, which is of great concern in infertility treatment.[8]

Al-Fadhli et al compared the regimen of 2.5 mg doses and 5 mg letrozole. They found that the average number of mature follicles and the pregnancy rates were significantly higher in patients receiving 5 mg of letrozole.[6] Thus, our study aims to compare the effects of different doses of letrozole, i.e., 2.5 mg vs. 5.0 mg daily, in women undergoing controlled ovarian hyperstimulation.

METHODS

After Approval of the "Institutional Protocol Committee" and "Ethics committee," this Randomized Controlled trial was conducted for one year from 19/06/2021-19/06/2022 in the Department of Obstetrics and Gynecology at Dr. Rajendra Prasad Government Medical College, Kangra at Tanda. The couples attending the infertility clinic suffering from primary or secondary infertility lasting for at least one year and consenting to participate in the study were enrolled in the study.

Inclusion criteria

Married women from 18- 40 years of age, infertility with a history of unprotected sexual intercourse for at least one year., normal semen parameters per W.H.O. guidelines (2010) and patent tubes on hysterosalpingogram or laparoscopy were included.

Exclusion criteria

Female with severe endometriosis (stage 4), women with untreated endocrinological disorders in the form of thyroid dysfunction, hyperprolactinemia and cushing syndrome and patients not willing to participate in the study were excluded.

The demographic and clinical details regarding the age, chief complaints with duration, obstetrical history, menstrual history, and personal history of the sampled women were recorded. All women underwent abdominal, speculum, and vaginal examinations following a general physical and systemic examination. The investigation included semen analysis, hormonal evaluation, baseline ultrasound of the pelvis, and hysterosalpingogram, and if needed, hysteroscopy and laparoscopy were done. Subjects were randomly assigned to one of two treatment groups of 30 each.

Group A: Women in this group received 2.5 mg of Letrozole from day 3-7 of menses along with gonadotropins

Group B: Women in this group received 5.0 mg of Letrozole from day 3-7 of menses, along with gonadotropins.

Injection Human Menopausal Gonadotropins (hMG) 75 I.U. i/m was given on day 7 and day 9 of the cycle. Patients were monitored by transvaginal ultrasound for follicular study from day 11 on every alternate day until hCG administration. The patient was then evaluated regarding the number and size of follicles and endometrial thickness. When one dominant follicle of size ≥18mm was visualized on ultrasound, hCG trigger with 5000 IU I.M. was given. Following this, IUI was done after 24-36 hours. The density gradient method and direct swim-up technique of sperm preparation were taken into practice. Patients were sent home under the support of micronized progesterone for 14 days. The pregnancy rates were calculated on the basis of positive results on a urine pregnancy test or a serum β hCG greater than 10 mIU/ml after a missed period. Transvaginal U.S.G. was done four weeks after a positive pregnancy test to confirm the presence of a gestational sac with fetal pole and fetal heart pulsation. A maximum of 4 cycles were tried. The mean and standard deviation of the measurement per group was used for statistical analysis. Differences between two groups was determined using student t test as well as Chi Square test and the level of significance was set at <0.05.

RESULTS

The mean age in group A 29.43 years and in group B was 28.72 years respectively as shown in Table 1. Also in group A 83.3% were in primary infertility, while 90% were in group B. It was observed that 22 patients (73.3%) in group A had been married for less than five years, and

eight patients (26.66%) were married for <10 years, whereas in group B, 20 patients (66.6%) were married for less than five years and 10 were (33.33%) married for less than ten years. In this study, all the women in both groups were euthyroid, and the mean value for S. TSH in group A is 2.59 mIU/L, and in the group, B is 2.84 mIU/L. The mean value of serum prolactin in group A was 13.68 ng/ml, and in the group, B was 14.94 ng/ml as in Table 1.

Table 1: The difference of mean age, S TSH and s. prolactin in different groups.

	Group A (n=30)	Group B (n=30)	P value
Mean age	29.43±3.31 yrs	28.72±3.64 yrs	0.828 (Student t test)
Mean S. TSH	2.59 mIU/L	2.84 mIU/L	0.391 (Student t test)
Mean S. prolactin	13.68 ng/ml	14.94 ng/ml.	0.286 (student t test)
Mean ET (mm)	7.39±0.88 mm	7.65±0.78 mm	0.03

In group A, 18 patients (60%), and in group B, 25 patients (83.3%) belonged sperm concentration in the range of 51-100 million/ml, whereas 12 patients in group A (40%) and 5 patients (16.6%) in group B has sperm count in the range of 15-50 million/ml. In group A, 25 patients (83.3%) and in group B, 20 patients (66.6%) had sperm motility <60%. Whereas 5 patients in group A and 8 in group B had sperm motility in range of 61-75% as shown in Table 2 and 3.

Table 2: Sperm concentration in the two groups.

Sperm concentration (million/ml)	Group A (n=30)		Group B (n=30)		P value (Chi-Square)
	No.	%	No.	%	
15-50	12	40	5	16.66	0.042
51-100	18	60	25	83.33	

Table 3: Sperm motility in two groups.

Sperm motility	Group A (n=30)		Group B (n=30)		P value (Chi-Square)
	No.	%	No.	%	
<60%	25	83.33	20	66.66	
61-75%	5	16.66	8	26.66	0.197
>75%	0	0	2	6.66	

Table 4: Number of ovulation induction cycles in the two groups.

	Group A (n=30)	Group B (n=30)
No. of induction cycles	78	83
Cycles with ovulation	61	78
Cycles cancelled	17	5
No of cycles of IUI given	61	78
Ovulation rate per cycle (%)	78.2%	93.97%
Total conception	4/30	4/30

In group A, out of 78 induction cycles, 61 were ovulatory (78.2%), and in group B, out of 83 induction cycles, 78 were ovulatory (93.97%). Thus, a slightly higher ovulation rate was seen in group B, taking 5 mg letrozole as compared to group A as shown in Table 4.

In group A, 12 patients had endometrial thickness >7 mm (40.3%), and in group B, 22 patients (73.66%) had E.T.>7mm. Mean E.T. was 7.39 mm in group A and that in group B was 7.65. Thus, there was a significant difference in endometrial thickness between the two groups as seen in Table 1.

Table 5: Pregnancy rate per cycle of IUI in the two groups.

Cycle	No. of couples		Pregnancy during cycle		Pregnancy rate per cycle of IUI (%)	
	Group A	Group B	Group A	Group B	Group A	Group B
1	30	30	2	1	6.66	3.33
2	27	29	2	2	7.4	6.9
3	18	21	0	1	0	4.76
4	3	3	0	0	0	0
Total	78	83	04	04	5.1%	4.8%

In both the groups, the pregnancy rate was found to be 13.33%; thus, no difference was there in conception rates between both groups. In both the groups, none of the patients had ovarian hyperstimulation syndrome.

In group A, the total number of induction cycles was 78, out of which IUI was done in 61 cycles, whereas in group B, the total number of induction cycles was 83, and IUI was done in 78 cycles. The pregnancy rate per IUI cycle was observed to be 5.1% in group A and 4.8% in group B. Thus, the pregnancy rate was almost equal in both group as shown in Table 5 and Figure 1.

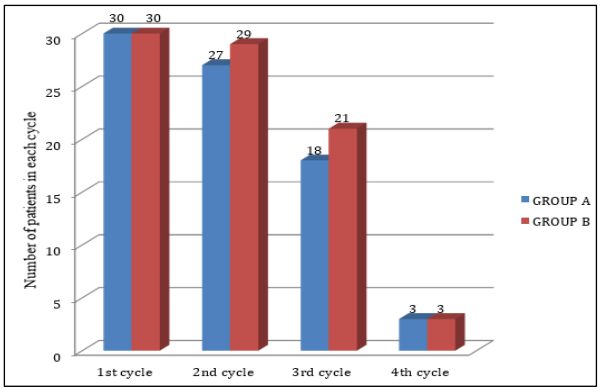

Figure 1: Number of IUI performed in each cycle.

DISCUSSION

Despite several studies that have shown the effectiveness of letrozole for ovulation stimulation there have been very few studies to determine the optimal dose. Fadhli et al conducted a prospective randomized trial comparing 2.5 mg and 5.0 mg letrozole found that 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).[6]

Badaway conducted a study aimed at comparing the three most commonly used doses: 2.5, 5, and 7.5 mg. reports a significantly higher (P<0.05) number of follicles (total, >14 mm and >or = 18 mm) on the day of administration of human chorionic gonadotrophin in the 7.5 mg group, associated with significantly fewer (P<0.05) days of stimulation.[9]

In a study by Masroor et al reported the mean age of patients in the letrozole 2.5 mg group to be 31.12 years and in the 5.0 mg letrozole group to be 30.85 years which corresponds to the mean age in our study.[10]

In a study by Gayam et al, primary infertility was to be seen in 75% of patients in the group receiving 2.5 mg vs. 66.6% in the 5.0 mg letrozole group, which is less as compared to our study.[11] The mean duration of marriage in group A and that in group B were found to be similar in our study. Portella et al, in a similar study, found no statistically significant differences in duration of infertility in patients taking letrozole 2.5 mg + rFSH and letrozole 5.0 mg + rFSH group that is 37.20 months and 47.02 months.[7]

In our study, normal semen parameters as per WHO 2010 criterion were included.

A retrospective cohort study by Findekle et al where IUI was performed over 5 years showed no correlation between the conception probability of IUI and the spermiogram parameters-concentration, density, and motility.[12]

In our study, the mean value of serum TSH and prolactin in group A was found to be 2.59±1.08 and 13.68±5.1in comparison to group B-2.84±1.14 and 14.94±3.92, respectively.

In a similar study by Masroor et al, the population had an average hormonal assay with high TSH observed in 35% and 21.67% of 2.5 mg and 5 mg. Study groups and high prolactin levels were seen in 16.67% and 6.67% of patients in 2.5 mg and 5 mg study groups, respectively.[11]

In the present study, the ovulation rate in group B (93.97%) was found to be higher than group A (78.2%), receiving 2.5 mg of letrozole.

Yang et al, in a study of PCOS women receiving 5.0 mg letrozole, both the number of mature follicles and pregnancy rate were significantly higher than those in women having the half dose (P<0.05).[13]

The optimum follicle size in the present study is >18 mm for ovulation. In our study, the mean follicle size in group A was found to be 17.39 mm, and that in group B was 18.56 mm. The mean number of follicles with a diameter ≥18 mm was higher in the group receiving 5 mg letrozole (1.64±0.91) compared to the group receiving 2.5 mg letrozole (1.37±0.56). Still, statistically, there was no significant difference (p = 0.134) in a study by Tobing et al.[14]

The mean endometrial thickness in group A was found to be 7.39 mm, and that in group B was found to be 7.65 mm, which was statistically significant. In a similar study by Yang et al, the thickness of the endometrium was identical between the two groups receiving 2.5 mg and 5.0 mg of letrozole.[13]

In the present study, the clinical pregnancy rate was found to be 13.3 % in both groups A and group B. In a study by Elhousseiny, it seems that the use of higher doses of letrozole improves endometrial thickness and follicle number. Still, it offers no advantage in terms of pregnancy rates over the lower (2.5 mg) dose.[15]

Thus, a slightly higher ovulation rate was seen in group B, taking 5 mg letrozole as compared to group A. The pregnancy rate was found to be 5.12 % in group A which was comparable to that in group B, 4.81%. Higher pregnancy rates were found in the initial 2 cycles of IUI in both groups. In a study by Michau et al, the clinical pregnancy rate after the first IUI was 15%, 13% after the second, and 10% after the third. Pregnancy occurred in 34.7% of cases after the first IUI, 29.5% after the second, and 17.15% after the third, for a cumulative rate of 81.4% after three trials. The pregnancy rates per IUI after the fourth trial were lower than 9%.[16]

The study was based on the sample observations collected from only 60 women due to time and resources at the disposal of the researcher. The results could be

further refined and improved by increasing the sample size and trying a more significant number of protocols to enhance the scope of the study.

This study has some limitations. The present study has been carried out systematically using scientific methodology. Every care has been taken to select the sample and follow standard techniques. The accuracy of data was ensured through individual care and personal attention. The study was based on the sample observations collected from only 60 women due to time and resources at the disposal of the researcher. The results could be further refined and improved by increasing the sample size and trying a more significant number of protocols to enhance the scope of the study.

CONCLUSION

Two treatment protocols were adopted in the present study, comparing the effects of two different doses of letrozole for ovulation induction in patients undergoing IUI. It is concluded from this study that higher ovulation rates are observed with letrozole 5 mg as compared to 2.5 mg. There is no difference in pregnancy rates between the two groups.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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