

## Comparison of efficacy of letrozole and clomiphene citrate for induction of ovulation

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### Abstract

**Background and objective:** Ovulatory dysfunction is a common cause of infertility. This study aimed to determine if letrozole is more efficient than clomiphene for the induction of ovulation in a group of unovulatory infertile women.

**Methods:** A prospective, comparative study was conducted at the Fertility Center Out-patient Department of Maternity Teaching Hospital, Erbil city, Kurdistan Region, Iraq, from May 2011, to May 2012. Hundred infertile couples having anovulatory infertility were included in the study; 50 women (146 cycles) were given letrozole 5 mg for three cycles, and 50 (148 cycles) women were put on clomiphene citrate (CC) 100 mg for three cycles, from day 2 to day 6 of the menstrual cycle. The diagnosis of pregnancy was confirmed by ultrasound. Two-tailed independent t-test was used to compare means, while proportions were compared with the Chi-Square test.

**Results:** Ovulation occurred in 131/150 women in the clomiphene citrate group and 124/150 women in the letrozole group. The total number of mature follicles for clomiphene citrate was  $1.44 \pm 0.56$ mm, while it was  $1.13 \pm 0.32$ mm for letrozole, which was highly significant ( $P = 0.001$ ). Endometrial thickness at the time of hCG administration for clomiphene citrate versus letrozole was ( $7.95 \pm 1.53$ mm versus  $9.37 \pm 2.04$ mm,  $P = 0.001$ ) respectively. The pregnancy rate was 16/148 cycles in the clomiphene citrate group and 20/146 cycles in the letrozole group.

**Conclusion:** Letrozole and clomiphene citrate are equally effective for the induction of ovulation and achieving pregnancy in patients with anovulatory infertility.

**Keywords:** Letrozole; Clomiphene Citrate; Ovulation; Pregnancy.

### Introduction

Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility. Clomiphene citrate is considered as the drug of choice for first line treatment of anovulatory dysfunction for a variety of reasons. It is orally administered, has few side effects, is readily available, and is inexpensive. Although ovulation rates are in the range of 70-80%, the actual pregnancy rates are significantly lower at around 30-40%. Clomiphene resistance, together with side effects like multi-follicular development and cyst formation, are areas of concern. The desire for an effective alternative persists.<sup>1</sup>

The need for an alternative to clomiphene citrate (CC) for ovulation induction (OI) was realized since the 1990s. CC had antiestrogenic effects on the endometrium on the cervical mucus and the prolonged accumulation in tissues leading to prolonged depletion of estrogen receptors. This could result in hot flashes, perimenopausal symptoms.<sup>2</sup> Letrozole, an aromatase inhibitor, was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance.<sup>3,4</sup> Letrozole is an orally active third-generation aromatase inhibitor most commonly used for ovulation

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induction. It has been in use for a few years now, and a number of researchers have studied this molecule as an option for ovulation induction. Letrozole acts by reducing estrogen production by blocking androgens to estrogens conversion. Additionally, it has no adverse effect on the endometrium and cervical mucus. When compared with clomiphene citrate, letrozole has a much shorter half-life and hence minimal suppressive effect on the endometrium. The recommended regimen is 2.5–5 mg per day for five days commencing in the first five days of spontaneous or induced bleeding, or as a single dose of 20 mg on day 3 of the period. The monitoring is similar to that of clomiphene citrate. The use in ovulation induction, however, is an off-label use.<sup>5-8</sup> According to the best knowledge of the researchers, this research is regarded as the first to be conducted in the IVF center of the Maternity Teaching Hospital to determine the efficacy of letrozole versus clomiphene citrate for management of women with anovulatory cycles.

## Methods

A prospective comparative study was conducted in the Fertility center Out-patient department of Maternity Teaching Hospital, Erbil, from May 2011 to May 2012. The study included all the anovulatory women who previously diagnosed and who required ovulation induction. A total of 100 patients were included in the study; that underwent 293 stimulation cycles for ovulation induction. Letrozole group (Group I), comprising of 50 patients, had 146 cycles of the aromatase inhibitor letrozole. Clomiphene citrate group (Group II), comprising of 50 patients, underwent 148 cycles of clomiphene. Both groups were administered five days of a fixed dose of letrozole and clomiphene, respectively, starting day 2 of their cycle; if the patient had delayed menstrual cycle medroxyprogesterone was administered to induce menses. Ultrasonography was performed on day 9 of the cycle, and

follicular number, follicular size, and endometrial thickness and pattern were determined; follicles were measured in two perpendicular dimensions and the mean value recorded, while endometrial thickness was measured at the point of greatest thickness. Follicular size  $\geq$  18 mm on day 9 of the menstrual cycle. 10,000 IU of human chorionic gonadotropin (hCG) was administered. Quantitative  $\beta$ hCG was done two weeks after hCG injection to diagnose chemical pregnancy. Clinical pregnancy was confirmed by observing a gestational sac with fetal echoes and pulsation four weeks after a positive pregnancy test by transvaginal ultrasound. Patients receiving therapy outside the study period were excluded from the study.

## Inclusion criteria

The inclusion criteria included women aged 20- 45 years, infertility due to anovulation, patients desiring to conceive, and require fertility medications and accept to participate in the trial. The protocol was approved by the Research and Ethical Committee of Hawler Medical University, College of Medicine. Verbal informed consent was obtained from the participants of this study.

## Statistical analysis

Statistical analysis were performed using SPSS version 18. Two-tailed independent t-test was used to compare means, and the proportion was compared with the Chi-Square test. A *P* value of  $<0.05$  was considered significant.

## Results

Table 1 shows the characteristics of the 100 women who participated in the study. There were no significant differences observed in regard to mean ages and primary and secondary infertility between the studied groups. Table 2 demonstrates the outcomes in terms of endometrial thickness, serum estradiol, mean numbers of follicle formation between the letrozole and clomiphene citrate groups.

**Table1:** Demographic characteristic of patients in both study groups (letrozole versus clomiphene citrate)

	Clomid		Letrozole		Total		P value
	No.	(%)	No.	(%)	No.	(%)	
<b>Age</b>							
< 25	20	(40.0)	19	(38.0)	39	(39.0)	0.921
25-29	9	(18.0)	11	(22.0)	20	(20.0)	
30-34	10	(20.0)	8	(16.0)	18	(18.0)	
≥ 35	11	(22.0)	12	(24.0)	23	(23.0)	
<b>Mean (<math>\pm</math> SD)</b>	28.46	( $\pm$ 6.92)	28.56	( $\pm$ 7.12)			0.943
<b>Duration of infertility</b>							
< 5	25	(50.0)	25	(50.0)	50	(50.0)	0.820
5-9	17	(34.0)	19	(38.0)	36	(36.0)	
≥ 10	8	(16.0)	6	(12.0)	14	(14.0)	
<b>Mean (<math>\pm</math> SD)</b>	5.54	( $\pm$ 3.55)	5.12	( $\pm$ 2.95)			0.521
<b>Type of infertility</b>							
Primary	30	(60.0)	33	(66.0)	63	(63.0)	0.534
Secondary	20	(40.0)	17	(34.0)	37	(37.0)	
<b>Total</b>	50	(100.0)	50	(100.0)	100	(100.0)	

A P value of <0.05 was considered significant.

**Table 2:** Main outcome measure between both study groups (letrozole versus clomiphene)

	Clomid		Letrozole		P value
	Mean	( $\pm$ SD)	Mean	( $\pm$ SD)	
Number of mature follicles produced during HCG injection	1.44	(0.56)	1.13	(0.32)	0.001
Endometrial thickness at the time of HCG injection	7.95	(1.53)	9.37	(2.04)	<0.001
Estrogen level at HCG injection	356.10	(122.32)	234.50	(64.75)	<0.001

HCG: Human chorionic gonadotrophin

A P value of <0.05 was considered significant.

Table 3 shows the number of cycles in each letrozole and clomiphene citrate groups with statistically significant differences between the two groups. Table 4 demonstrates that proportions of women who ovulated in the first, second, and third cycles in the two treatment groups with no statistically significant difference. Pregnancy occurred in 16% in

the clomiphene citrate group and 20% in the Letrozole group, while the difference was statistically not significant ( $P = 0.603$ ). Two twin pregnancies occurred in the clomiphene citrate group and none in the letrozole group. No higher order pregnancies or OHS occurred in both groups (Figure 1)

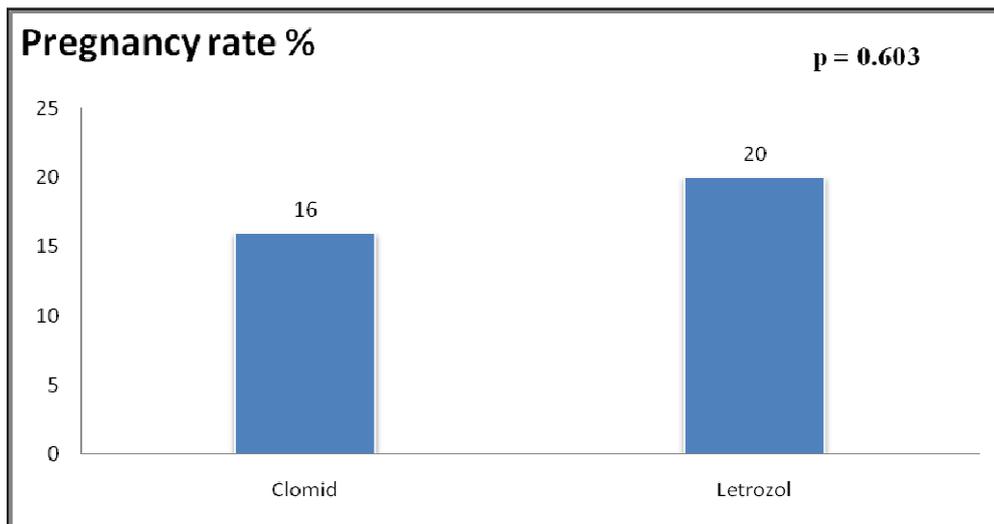
**Table 3:** Number of cycles in each group per 150 cycles.

	Clomiphene citrate		Letrozole		Total		P value
	No.	(%)	No.	(%)	No.	(%)	
Two cycles	2	(4.0)	4	(8.0)	6	(6.0)	0.678*
Three cycles	48	(96.0)	46	(92.0)	94	(94.0)	
Total	50	(100.0)	50	(100.0)	100	(100.0)	

\*By Fisher's exact test.

**Table 4:** Proportions of women who ovulated in the first, second, and third cycles.

	Clomiphene citrate N = 50		Letrozol N = 50		Total N = 100		P value
	No.	(%)	No.	(%)	No.	(%)	
Ovulation in the first cycle	40	(80.0)	37	(74.0)	77	(77.0)	0.476
Ovulation in the second cycle	45	(90.0)	42	(84.0)	87	(87.0)	0.372
Ovulation in the third cycle	46	(92.0)	45	(90.0)	91	(91.0)	0.727



**Figure 1:** Pregnancy rate in the two study groups.

Among side effects reported in 50 subjects who received clomiphene citrate, four people (8%) reported blurred vision, six patients (12%) headache, six patients (6%) nausea, and two (4%) twin pregnancies were observed. However, no complications were reported in the group receiving letrozole. No serious side effects were reported in either group.

## Discussion

Numerous original articles, reviews, and meta-analysis have been published. In women with failure or resistance to CC, letrozole was shown to be very effective both in ovulation rate and live birth rate. The year 2005, show a major setback to the use of Letrozole in infertile women.<sup>9</sup> In recent practice, letrozole is considered an alternative to clomiphene in ovulatory and nonovulatory infertile women. This drug can induce ovulation in 62% of clomiphene-resistant patients and can result in pregnancy in 14.7% of these cases. Moreover, the use of letrozole has been recommended for patients who ovulate with clomiphene but have a thin endometrium.<sup>3,10</sup> In the present study, no statistically significant difference was observed regarding ovulation or pregnancy rates between the two groups. However, the pregnancy rate was slightly higher in letrozole than the clomiphene group (20/146 cycle versus 16/148 cycle, respectively). Ovulation occurred in 131/148 (88.5%) in clomiphene citrate group and 124/146 (84.9%) in letrozole group, which is comparable to that reported recently by Badawy et al.,<sup>11</sup> who had an ovulatory rate of 62% for letrozole cycles, also agreed with the study done by Badawg et al.,<sup>12</sup> in which ovulation occurred in 365 out of 540 cycles (67.5%) in the letrozole group and 371 out of 523 cycles (70.9%) without a statistically significant difference. In contrast, it does not go with Mosammat et al. study. Twenty (62.5%) patients from the letrozole group and 12 (37.50%) patients from the clomiphene citrate group ovulated during the

observation period,<sup>13</sup> also the same with Nahid et al. study ovulation rate was 88%; similar in both groups,<sup>14</sup> but agree with Ahmed et al. study Ovulation occurred in 365 out of 540 cycles (67.5%) in the letrozole group and 371 out of 523 cycles (70.9%) without a statistically significant difference,<sup>15</sup> that is mean letrozole has comparable efficacy clomiphene citrate regarding ovulation in most of the literature and some of them even higher ovulation rate.<sup>5,13-16</sup> The pregnancy rate in current study per cycle was 16/50 in the letrozole group and 20/50 in the clomiphene citrate group which is there is no statistically significant difference between the groups, agree with Ahmed et al. study, the pregnancy rate per cycle was 15.1% in the letrozole group and 17.9% in the clomiphene citrate group without statistical difference between the groups,<sup>15</sup> and also goes with Mosammat et al. study. Thirteen patients from the letrozole group (40.63%) and six patients from the clomiphene citrate group (18.75%) became pregnant,<sup>13</sup> and Nahid et al. study, the pregnancy rate in both groups was almost similar while disagreeing with Moustafa et al. study, the clinical pregnancy rate was significantly higher in letrozole group (23.07 vs. 10.68 %,  $P < 0.001$ ).<sup>13-16</sup> In Moustafa et al, study include letrozole group ( $n = 136$ ) and clomiphene citrate group ( $n = 134$ ). The mean number of mature follicles was significantly higher in clomiphene citrate group ( $2 \pm 0.9$  vs.  $1 \pm 0.0$ ,  $P = 0.02$ ), which agrees with the result of the current study which has a mean number of mature follicles in clomiphene citrate group versus letrozole group ( $1.44 \pm 0.56$  versus  $1.13 \pm 0.56$ ) respectively with highly significant difference between both group ( $P = 0.001$ ), also goes with the result of Ahmed B et al. study comparing letrozole group include (218 patients, 545 cycles) and clomiphene citrate group (220 patients, 518 cycles). The total number of follicles was statistically significantly greater in the clomiphene citrate group ( $6.8 \pm 0.3$  versus  $4.4 \pm 0.4$ ). While Nahid study

includes two groups, 50 patients who received letrozole and clomiphene citrate. The average number of follicles in the group receiving clomiphene citrate was  $58/1 \pm 32/2$ , and in the group receiving letrozole it was  $50/0 \pm 30/1$ , which does not go with the result of the current study, the difference was not significant.<sup>13,15,16</sup> In current study endometrial thickness at the time of hCG administration was statistically significantly greater in the letrozole group ( $9.37 \pm 1.37$  mm versus  $7.95 \pm 1.53$  mm,  $P < 0.001$ ), which is comparable with the result of Moustafa et al. study in which endometrial receptivity in letrozole group as assessed by the endometrial thickness and Doppler flow indices of uterine and subendometrial vessels, also goes with the result of Ahmed B et al. study Endometrial thickness at the time of hCG administration was statistically significantly greater in the clomiphene citrate group ( $9.2 \pm 0.7$  mm versus  $8.1 \pm 0.2$  mm), also goes with the result of Payal et al. study as the mean endometrial development was  $8.72 \pm 1.41$  mm in the letrozole and  $8.78 \pm 1.16$  mm in the clomiphene group ( $P = 0.004$ ). However, the current study disagrees with Nahid et al. study regarding the mean endometrial thickness on the day of hCG administration was  $27/1 \pm 71/9$ , and in the group receiving clomiphene citrate it was  $06/3 \pm 08/6$ , and the difference was statistically not significant.<sup>15-17</sup> About mean serum  $E_2$  level was  $356.10$  pg/mL and  $234.50$  pg/mL in the clomiphene citrate and letrozole groups, respectively in current study higher in clomiphene citrate group, goes with the result of the majority of studies including Moustafa et al., Mosammat et al., Nahid et al. study and Payal et al. study, there are significant difference statistically.<sup>13,14,16,17</sup> Regarding side effects, there were no significant side effect reported in both study groups in the current study reported which does not goes with the result of Moustafa et al. study.<sup>13</sup> Also in Nahid study the side effects reported by patients in the group receiving clomiphene citrate were higher, while in the

group receiving letrozole no complication was reported.<sup>14</sup> Based on these findings, letrozole can be considered an appropriate alternative for clomiphene citrate without side effects.<sup>13,16</sup>

### Conclusion

Our findings suggest letrozole and clomiphene citrate are equally effective for the induction of ovulation and achieving pregnancy in patients with un ovulatory cycles. Also, the side effects reported by patients in the group receiving clomiphene citrate were higher. Based on these findings, letrozole can be considered an appropriate alternative for clomiphene citrate without side effects. However, the quality of medical evidence supporting aromatase inhibitors for OI, are inadequate.

### Competing interests

The authors declare no competing interests.

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