

## Comparing the effect of clomiphene citrate and letrozole on ovulation induction in infertile women with polycystic ovary syndrome

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### Abstract

**Objective:** To compare the effects of letrozole and clomiphene citrate in women with polycystic ovaries.

**Methods:** The double-blind randomised clinical trial study was conducted from September 22, 2012 to March 20, 2013, at the Islamic Azad University of Medical Sciences, Mashad, Iran, and comprised infertile women with polycystic ovaries. The subjects were classified into two groups. Patients who received letrozole 5mg tablets per night formed group A, and those who received clomiphene citrate 50mg tablets per night formed group B. The medication continued for 3-7 days in each group. On the 13th day, transvaginal sonography with multi-frequency vaginal probe was done to check the number and the size of dominant follicle and endometrial thickness. Human chorionic gonadotrophin 5000 IU ampoule, 10000 IU per night, was administered intramuscularly for ovulation in the case of dominant follicle over 18mm and the insemination was recommended 24-36h after injection. Beta human chorionic gonadotrophin was determined 16 days after the injection by immunoassay technique. The patients were followed up for 12 months. SPSS 16 was used for data analysis.

**Results:** There were 220 patients; 110(50%) in each of the two groups. The mean age of patients in group A was 26.2±3.6 years and that in group B was 27±3.6 years. Endometrial thickness in group A was significantly greater compared to group B (p=0.001). The clinical consequence of drug use (pregnancy) in group A was better than group B (p=0.007).

**Conclusion:** Although more clinical studies are needed, letrozole is recommended for women with polycystic ovaries and those resistant to clomiphene citrate.

**Keywords:** Infertile women, Polycystic ovary syndrome, Letrozole. (JPMA 70: 268; 2020)  
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### Introduction

Polycystic ovary (PCO) is an endocrine disorder in women and it is the reason for infertility due to the absence of ovulation. The disease affects 5% of women.<sup>1,2</sup> PCO is a disorder that can affect the function of the ovary so that the average level of luteinising hormone (LH) becomes higher than the regular level and the follicle stimulating hormone (FSH) becomes lower compared to the healthy women. Increase of the FSH secretion from the Hypofizgland is necessary for the growth of follicles and steroids.<sup>3,2</sup> High serum level of LH causes an increase in androgens' secretion and inhibits the induction of FSH for LH receptors in follicles, and, therefore, the dominant follicle is not created.<sup>3,2</sup>

Some symptoms related to PCO include obesity, malfunction of menstruation and infertility separately or simultaneously.<sup>4</sup> Generally, infertility is defined as couples' uncontrolled sexual intercourse without pregnancy occurrence.<sup>2</sup> About 10-15% of the couples in .....  
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the age of fertility are faced with barrenness.<sup>5</sup> In a study, the problem of barrenness in the western parts of Tehran, Iran, was 12%; but 87.3% of all the women under study didn't have fertility problems.<sup>6</sup> The first line of medical treatment is the use of clomiphene citrate which acts as an antagonist oestrogen.<sup>7</sup> The side effects of clomiphene citrate are not dependent on the amount of dosage and they may appear with the lowest intake. The most popular unknown effects include the hotness of vasomotor (10%) bigness of the ovaries that can be returned, fluctuation (blowing stomach), nausea and vomiting, pain and sensitivity of the breasts, headache and falling of the hair that can be returned, sleeplessness and depression (1.5%).<sup>8</sup>

In 7-10% of cases which use clomiphene citrate, multiple pregnancy happens. In descriptive studies, the prevalence of ectopic pregnancy following clomiphene administration is 4.5-1.5%.<sup>8</sup> Also, some studies showed a relationship between the use of clomiphene citrate and ovary cancer<sup>8</sup> and 25% of PCO patients were resistant to clomiphene citrate treatment.<sup>9,7</sup> Regarding the mentioned problems, it is suggested that letrozole be used in the patients with PCO. Letrozole is an aromatase controller and the potential treatment line in PCO women. Clomiphene citrate may have direct environmental anti-oestrogenic effects in some

people while letrozole did not show such effects.<sup>3</sup>

One 2010 study showed that Letrozole with a short lifetime had a better effect in endometrium and it was very effective in people with long-time infertility and low ovulation.<sup>10</sup> In a 2008 study on PCO women resistant to clomiphene citrate, Letrozole therapy for fertility was more effective than clomiphene citrate treatment even though it was not statistically significant.<sup>11</sup> The current study was planned to investigate the effect of Clomiphene citrate in comparison with Letrozole in PCO women.

## Patients and Methods

The double-blind randomised clinical trial (RCT) study was conducted from September 22, 2012, to March 20, 2013, at the Islamic Azad University of Medical Sciences, 22 Bahman hospital in Mashhad, Iran. Approval was obtained from the institutional ethics committee, and written informed consent was taken from the subjects. The sample size was calculated on the basis of a previous study.<sup>12</sup> Those included were PCO infertile women aged 18-40 years who had absence of ovulation (oligomenorrhea, amenorrhea), symptoms of increase in androgen in the blood (acne, hirsutism) and the laboratory symptoms of androgen increasing (increase in testosterone (TST) and Dehydroepiandrosterone (DHEA),<sup>2</sup> and with body mass index (BMI) less than 35.

Those with other infertility reasons, such as infertility in the partner, infertility duration more than 5 years, women with ovary cyst and internal pathology of the endometrium, active malignancy of the breast and the ovary, and individuals who avoided using aromatase inhibitor and oestrogen receptor modulator were excluded.

At first, researchers drew a chart including 240 rows (001-240). Then, we carried out an allocation to the control and sample group using the table random numbers. Patients were divided into 2 groups: control group (n=120) and sample group (n=120). Names and characteristics of patients were allocated to each group, and only the researchers were aware of this table, and the patients did not know about the drug.

The participants were randomised into two groups. Patients who received Letrozole 5mg tablets per night were in group A, and those who received clomiphene citrate 50mg tablets per night were in group B. The medication lasted 3-7 days in both groups.

Before administration, sonography was performed to identify the thickness of endometrium (the third day). In group B, two 50mg tablets (Iran Hormone Company) were used every night from the 3<sup>rd</sup> to the 7<sup>th</sup> day of menstruation, and in group A, two 5mg tablets (Iran Hormone Company)

were used every night from the 3<sup>rd</sup> to the 7<sup>th</sup> day of menstruation. On the 13<sup>th</sup> day of menstruation, transvaginal sonography was done with multi-frequency vaginal prop (20 Madison V) to investigate the number and the size of follicle and the thickness of the endometrium. Human chorionic gonadotrophin (hCG) ampoule (Daru Pakshh IU 5000,10000 IU) was used daily for ovarian function in the case of dominant follicle over 18mm, and sexual intercourse between 24-36 hours post-injection was recommended. Sixteen days after the injection, beta hCG ( $\beta$ HCG) was investigated through immunoassay. Measurements of prolactin (PRL), DHEA, Thyroid stimulating hormone (TSH) and TST were also done for all patients. The patients were followed up for 12 months.

Data were analysed using SPSS 16. Parametric dependent and independent t-test and non-parametric Mann-Whitney test were used to compare the two groups. The odds ratio (OR) and 95% confidence interval (CI) were also estimated.  $P < 0.05$  was considered statistically significant.

## Results

Of the 240 subjects approached, 8(3.3%) were excluded for

**Table-1:** Demographic data of participants.

| Group Variable                 | Clomiphene     | Letrozole      | Result |
|--------------------------------|----------------|----------------|--------|
| Body mass index                | 27.3 $\pm$ 1.8 | 27.6 $\pm$ 1.8 | NS     |
| Duration of infertility (year) | 2.4 $\pm$ 1.3  | 2.1 $\pm$ 1.2  | NS     |
| Duration of marriage (year)    | 3 $\pm$ 1.9    | 2.6 $\pm$ 1.3  | NS     |

NS: Not significant.

**Table-2:** Comparison of endometrium thickness, number of follicles and the size of follicles between the two groups.

| Factors investigated | Endometrium thickness<br>Average $\pm$ SD | Number of follicles<br>Average $\pm$ SD | Size of follicles<br>Average $\pm$ SD |
|----------------------|---|---|---------------------------------------|
| Group                |   |   |                                       |
| Clomiphene           | 8.3 $\pm$ 2.6                             | 1.3 $\pm$ 0.4                           | 18.8 $\pm$ 1.5                        |
| Letrozole            | 11.8 $\pm$ 2.7                            | 1.4 $\pm$ 0.6                           | 19.3 $\pm$ 1.6                        |
| Results              | $P^* = 0.001$                             | $P^* = 0.152$                           | $P^* = 0.13$                          |

\*Mann Whitney test

There was no significant difference in terms of the number and the size of the follicles

**Table-3:** Comparison of the clinical result of Letrozole and Clomiphene therapy.

| Pregnancy Group | Yes<br>Numbers (percentage) | No<br>Numbers (percentage) | Test result   |
|-----------------|-----------------------------|----------------------------|---------------|
| Clomiphene      | 27(24.5)                    | 83(75.5)                   | $P^* = 0.007$ |
| Letrozole       | 45(40.9)                    | 65(59.1)                   |               |
| Total           | 72(32.7)                    | 148(67.3)                  |               |

\*Chi Square test

The probability of pregnancy occurrence in group A was relatively more than group B ( $p = 0.007$ )

**Table-4:** Association between the type of medications in PCO women and pregnancy.

| Cases under study | Result of the experiment | Number | Result of pregnancy based on group |           |                 |           | P value |
|-------------------|--------------------------|--------|------------------------------------|-----------|-----------------|-----------|---------|
|                   |                          |        | Clomiphene group                   |           | Letrozole group |           |         |
|                   |                          |        | Yes (%)                            | No (%)    | Yes (%)         | No (%)    |         |
| TST nmol/L        | >3                       | 90     | 15(16.66)                          | 60(66.66) | 8(8.88)         | 7(7.08)   | 0.001   |
|                   | 1.9-2.9                  | 56     | 3(5.35)                            | 14(25)    | 18(32.14)       | 21(37.5)  | 0.07    |
|                   | 1.8-0.5                  | 74     | 9(12.16)                           | 9(12.16)  | 19(25.67)       | 37(50.01) | 0.26    |
| TSH ng/dl         | >10                      | 34     | 6(17.64)                           | 18(52.49) | 3(8.82)         | 7(20.6)   | 1.00    |
|                   | 10-5                     | 20     | 0(0)                               | 11(55)    | 6(30)           | 3(15)     | 0.002   |
|                   | 5>                       | 166    | 21(12.65)                          | 54(32.53) | 36(21.68)       | 55(33.23) | 0.14    |
| DHEA µg/dl        | >400                     | 50     | 6(12)                              | 36(72)    | 0(0)            | 8(16)     | 0.57    |
|                   | 400-270                  | 18     | 3(16.66)                           | 3(16.66)  | 3(16.66)        | 9(50.02)  | 0.34    |
|                   | 45-270                   | 152    | 18(11.84)                          | 44(28.94) | 42(27.63)       | 48(31.59) | 0.038   |
| PRL ng/dl         | >20                      | 28     | 7(25)                              | 16(57.14) | 5(17.86)        | 0(0)      | 0.54    |
|                   | ≤20                      | 192    | 22(11.45)                          | 63(32.81) | 45(23.45)       | 62(32.29) | 0.01    |

PCO: Polycystic ovary

TST: Testosterone

TSH: Thyroid-stimulating hormone

DHEA: Dehydroepiandrosterone

PRL: Prolactin.

not meeting the criteria. In the follow-up stage, 12(5%) more patients were lost, and the final sample stood at 220(91.6%). There were 110(50%) patients each in groups A and B. The mean age of patients in group A was 26.2±3.6 years, and that in group B was 27±3.6 years ( $p>0.05$ ) (Table-1).

There was a statistically significant association between the type of medication and thickness of the endometrium ( $p=0.001$ ) and the endometrium thickness in group A was more than in group B. There was no significant difference in terms of the number and the size of the follicles (Table-2).

The probability of pregnancy occurrence in group A was relatively more than group B ( $p=0.007$ ) (Table-3).

There was no significant difference in the groups related to the incidence of miscarriage ( $p=1.00$ ) and there were 3(2.7%) such cases in both the groups. All 27(24.5%) successful cases in group B had a single pregnancy, but in group A, 42(38.2%) had single pregnancy and 3(2.7%) had multiple pregnancies ( $p=0.02$ ).

Outcome of TST, TSH, PRL and DHEA tests were also noted separately (Table-4).

## Discussion

Infertility is seen in 10-15% of couples and it is one of the most important causes that make individuals approach a gynaecologist. The present study investigated the effects of Clomiphene citrate and Letrozole on PCO women. There were 45 pregnancies among women using Letrozole and 27 among those using clomiphene citrate, and the difference was statistically significant. Also, the endometrium thickness

in Letrozole group was significantly more than clomiphene group. Various studies have compared the effect of these two medications. In 2012, a study observed that 53 of the individuals under Letrozole therapy needed 5mg of this drug from the 3rd to the 7th day of their menstruation while individuals under clomiphene therapy had to use 100mg during this period. After 2-3 mature follicles were observed in the sonography, 10,000 units of hCG hormone was administered and 36-40 hours later they performed intrauterine insemination (IUI) for them.<sup>13</sup> Our findings did not show any significant statistical difference regarding the pregnancy result between the two groups but pregnancy in Letrozole group was 22.6% and in clomiphene group it was 20.8%. A similar study showed 27.3% positive pregnancy test results in letrozole group and 18.2% in clomiphene group, but there was no significant difference between them.<sup>14</sup>

Another study on PCO women showed 16% pregnancy in Letrozole group and 13% in clomiphene group.<sup>15</sup> Furthermore, a study reported that ovulation in Letrozole group was 60% and in clomiphene group it was 32% ( $p=0.009$ ).<sup>16</sup> These studies were similar to our study and show that Letrozole is a more effective medication for PCO. In 2008, a study involved 218 patients who received 5mg Letrozole and 220 patients who received 100mg Clomiphene from the 3rd day of menstruation for five days. All the patients were examined by vaginal sonography to evaluate the average volume of follicles and endometrium thickness on the 10th, 12th and 14th days of their menstruation cycle, and then IUI was introduced. Pregnancy was established in 15% cases in the Letrozole group and

17.9% in the clomiphene group.<sup>17</sup> However, the endometrium thickness in Letrozole group was remarkably more than clomiphene group. Previous studies have shown that there is a direct relationship between endometrium thickness ( $>10.1\pm 3.5\text{mm}$ ) and higher chance of getting pregnant.<sup>18,19</sup> Another main factor in ovulation is the size of follicles so that when their size reaches 17-26mm, ovulation would happen.<sup>20</sup> There was no significant statistical difference between the number and the size of follicles in the participants of the current study, but the mean number and the size of follicles in Letrozole group was more. In one study, the thickness of endometrium in Letrozole group was  $9.44\pm 1.81$  and in clomiphene group it was  $6.43\pm 1.85$ <sup>15</sup> ( $p=0.001$ ). The above study is in agreement with our results. In studies about ovulation induction with clomiphene citrate, the incidence of miscarriage was 13-25% in one study, but there was no significant difference between the groups.<sup>8</sup> Also, PCO women who received Letrozole tablets had a little higher than the normal level of TSH, normal PRL and normal DHEA in their TST experiments than Clomiphene citrate and they were significantly different.<sup>8</sup> Letrozole is a good aromatase inhibitor for ovulation induction in PCO patients and it doesn't have negative effect on cervix mucus and increases the thickness of endometrium, the possibility of implantation and pregnancy as well. Also, the half-life of Letrozole is 45 hours which is shorter than clomiphene citrate and it prepares a better situation for ovulation and organogenesis than Clomiphene. Therefore, it seems that Letrozole can be used as the first-line treatment in PCO women with infertility problems. One of the major limitations of the current study we have not registered the Trial with an authorized office and we registered in Ethics committee of Islamic Azad university of Medical Sciences.

## Conclusion

Although more clinical studies are needed, results of the current study recommend the use of Letrozole in women with PCO and for those resistant to clomiphene citrate.

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**Conflict of Interest:** None.

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