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## Effects of Letrozole in Prevention of Premature Luteinizing Hormone (LH) Surge in Infertile Women with Clomiphene Citrate Resistant Polycystic Ovary Syndrome (PCOS) Undergoing Intrauterine Insemination

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### Abstract

**Background:** Polycystic ovarian syndrome (PCOS) is among the important causes of infertility in young women. Premature luteinizing hormone (LH) surge (PLS) is one of its complications. PLS can reduce the quality of oocytes and therefore decrease the success of intrauterine insemination (IUI). Letrozole, a non-steroidal aromatase inhibitor, prevents LH surge. In this study, we aim to evaluate the effects of letrozole on preventing premature LH surge in clomiphene-resistant patients with PCOS undergoing IUI. **Materials and Methods:** In this randomized clinical trial, 131 patients who were developed with PCOS were selected for IUI cycle, divided into two groups randomly: control group (n=67) and letrozole group (n=64). Incidence of premature LH surge, pregnancy, abortion and ongoing pregnancy rate, endometrial thickness and number of follicles were measured in both groups. **Results:** No significant difference was seen between mean ages in the two groups; 11.9% of the control group and 21.9% of the letrozole group became pregnant (P =0.005); furthermore, premature LH surge was seen in 4.7% of the letrozole group and 8.9% of the control group (P =0.003). E2 and Endometrial thickness was higher in letrozole group; however, LH was significantly higher in the control group (P =0.026). **Conclusion:** Administration of letrozole in clomiphene-resistant patients with PCO undergoing IUI cycle can decrease the incidence of PLS. In addition, it can increase pregnancy rate significantly. Therefore, using letrozole is more reasonable in patients who have not responded to clomiphene or are hypersensitive. [GMJ. 2015;4(3):104-11]

**Keywords:** Letrozole; Intra Uterine Insemination (IUI); Luteinizing Hormone; Pregnancy; Polycystic Ovary Syndrome

### Introduction

Infertility is a big challenge for people and governments; it can impose social, economic and psychological burden on the entire

society. Infertility is defined as failure to conceive despite having unprotected and frequent intercourse for a year [1]. Every year, many infertile couples are referred to infertility centers for treatment. Although many scientific

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advances have been made in this field, many concerns are remaining unknown; thus, thousands of couples are frustrated by these facilities.

Polycystic ovarian syndrome (PCOS) is a common cause of infertility [2]. PCOS is a multi-factorial syndrome which presents by a broad range of manifestations including metabolic, psychological and reproductive disorders [3]. The mechanism of infertility in PCOS is not yet clearly determined; however, defect in ovulation cycle which modulates through hypothalamus-pituitary-ovary axis is suggested to be one of the candidates for PCOS etiology mechanism [3, 4]. Therefore, one of the goals in treatment of these patients is inducing ovulation. Insulin sensitizing agents, selective estrogen receptor modulators, gonadotropins and aromatase inhibitors are some examples of medication therapy for this syndrome [5]. Premature luteinizing hormone (LH) surge is another phenomenon in this syndrome that can affect the quality of oocytes and pregnancy success [6]. Premature LH surge happens when LH concentration is  $>10$  mIU/ml and progesterone  $\geq 1$  ng/ml [7].

Clomiphene citrate (CC), a selective estrogen receptor modulator with peripheral anti-steroidal effects, is used widely as a first line therapy in infertile patients with PCOS. This drug inhibits estrogen receptors in hypothalamus and increases secretion of follicle stimulating hormone (FSH) by blocking negative feedback [8-11]. Some studies suggested that CC has suppressive effects on premature LH surge during controlling ovarian stimulation with gonadotropins [8, 12, 13]. Unfortunately, along with these positive features, it can cause many side effects such as decreasing the quality and quantity of cervical mucosa and endometrium (due to anti-steroidal effect), cardiovascular defects in fetus and ovarian hyperstimulation syndrome (OHSS) [11]. In addition, some patients are detected to be resistant to CC. Thus, alternative drugs are considered more and more in its therapy [14]. Letrozole, a third generation non-steroidal aromatase inhibitor, is one of these candidates. Letrozole can lead to a decrease in estrogen levels and its negative feedback affects central nervous system (CNS) increasing secretion of FSH

from pituitary gland and promoting follicle development [11, 15, 16]. Many researchers suggested that the effect of letrozole on PCOS was comparable with CC [17, 18]. Its side effects are also limited (GI upset, weakness and back pain) and can be better tolerated by patients [9]. Unlike CC, shorter in vivo half-life of letrozole causes lower plasma level at the end of follicular phase. So, small and immature follicles become atretic; as a result, the risk of OHSS in letrozole therapy is dramatically lower than CC therapy. The rates of multiple gestation and cardiac defects in fetus are also lower than CC. Moreover, this drug does not affect peripheral receptors; thus, no significant side effects on endometrium and cervix are reported till now. Furthermore, many studies have revealed that it is able to control premature LH surge [16, 19].

Letrozole has recently established a place in treatment of infertility caused by PCOS. Due to limited evidence, in this study we aim to evaluate the effects of letrozole on preventing premature LH surge in CC-resistant patients with PCOS undergoing IUI.

## Materials and Methods

### *Study Population*

This randomized clinical trial was performed among patients with CC-resistant PCOS who referred to the infertility center in Mother and Child hospital, a tertiary healthcare center for treatment. They underwent intra uterine insemination (IUI) between August 2011 and December 2012. We included 140 patients aged 18-35 with PCOS who had some properties that were referred below.

According to Rotterdam criteria [19], patients with at least 2 out of 3 of below criteria were included as a PCOS: 1- Chronic anovulation, 2- Clinical and/or biochemical evidence of hyperandrogenism and 3- polycystic appearance of ovaries in Transvaginal Ultrasound (TVS). Moreover, infertility was defined as failure to conceive despite having unprotected and frequent intercourse for at least 1 year. CC-resistance was considered as absence of ultrasound evidence regarding ovarian response consumption of 150mg of CC between the 5th and the 9th day of menstruation cycle for

three consecutive cycles.

The patients with breast cancer, renal and liver diseases, autoimmune problems and endocrinological problems such as diabetes, hyperprolactinemia, thyroid diseases, Cushing's syndrome and smokers were excluded from the study due to other related causes of infertility. None of them had a history of abdominal surgery.

Participants were banned from using any drugs that can affect carbohydrate metabolism (Metformin, Glybenclimide, etc.) including oral contraceptives in the last 2 months before this study. In addition, none of the patients received oral contraceptives, steroid hormone or any drugs interfering lipid metabolism such as Gemfibrozil and Atorvastatin as well as ovary, pituitary gland and hypothalamic function since 3 months prior to the study.

During our study, all patients received almost the same diet and exercise. Alcohol and alcoholic beverages were also forbidden. All participants had a documented normal blood test, renal function test, liver function test, hysterosalpingography (HSG) and negative pregnancy test before the study. Hormonal study including prolactin (to evaluate adenoma), thyroid stimulating hormone, FSH and LH were done in the 3rd day of cycle.

The partners should have at least two semen analyses. According to WHO, a normal semen analysis should have these properties: Sperm concentration  $\geq 15$  million/ml, total sperm count  $\geq 39$  million, mobility rate  $>40\%$ , progressive motility  $\geq 32\%$  and normal morphology  $\geq 4\%$  [20].

#### *Assays*

One hundred and forty patients who participated in this study were divided randomly into 2 groups: Control group (n=70) and Letrozole group (n=70). For all patients, complete history was taken, physical examination was done and positive findings were recorded in the questionnaires. Before starting the medication, TVS was done on the 3rd day of menstruation cycle for all of the participants. Blood samples were also taken for hormonal study. Following that, all of them received 75 IU/day highly purified recombinant FSH (Gonal-f, Serono, Hellas, Puregon, Greece)

intra muscularly, from the 3rd day through the day of human chorionic gonadotropin (HCG) injection. Moreover, members of Letrozole group received 5 mg/day letrozole (Razak Drug Laboratory, Tehran, Iran) since the 8th day of cycle up to the day of HCG injection. Since the 8th day of cycle, TVS was done every 2 or 3 days to monitor the size and the number of follicles. When at least two follicles became bigger than 18 mm and serum estradiol level lesser than 2000 pg/ml, HCG was injected. Endometrial thickness, LH and estradiol concentrations were also measured that day.

Estradiol levels higher than 2000 pg/ml were eliminated due to the risk of OHSS and 36 hours later, HCG injection IUI was done.

We performed IUI 36 hours after HCG administration. Furthermore, HCG was checked for documented pregnancies. Moreover, we performed TVS during the 6th and 7th weeks of pregnancy for better confirmation. This trial was registered in Islamic Republic Clinical Trials Database (IRCT2014010615102N2).

#### *Statistical Analysis*

All collected data were analyzed with SPSS version 14.0 using appropriate statistical parameters such as mean  $\pm$  SD, Range and percentages and tests such as T-test, Chi-square, one-way ANOVA and their non-parametric equivalent. P values less than 0.05 were considered as significant.

#### **Results**

In this study, 140 cases with PCOS resistant to CC were enrolled and divided into two groups of control (n=70) and letrozole (n=70). During this study, we eliminated 6 patients from the control group, 4 fell out of the study and 2 were finally diagnosed for OHSS. Three patients were also eliminated from the letrozole group; one fell out of the study protocol and 2 due to OHSS. Thus, 67 patients (age ranges 18-39 years) remained in control group and 64 cases (age ranges 21-37 years) remained in letrozole group. Demographic data, period of infertility, endometrial thickness, type of infertility and estradiol, luteinizing hormone, follicular stimulating hormone, thyroid stim-

ulating hormone and prolactin levels as well as premature secretion of luteinizing hormone were assayed in all patients, demonstrated in table-1.

Results of conducting IUI in infertile patients who had PCOS are presented in table-2. As seen, except abortion rate and number of big follicles, all IUI parameters had significant differences between letrozole and control groups.

## Discussion

PCOS is a common hormonal imbalance defect of reproductive ages in women. It can manifest by various complications; mostly infertility and chronic illnesses. Its etiology has not been determined yet; therefore, no definite treatment is found for infertility followed by PCOS [9]. One suggested etiology for infertility followed by PCOS is explained

**Table 1.** Basic data of 131 patients with polycystic ovarian syndrome resistant to Clomiphene citrate; P values from student t-test and Chi2. BMI: Body mass index, LH: luteinizing hormone, FSH: follicular stimulating hormone, TSH: Thyroid stimulating hormone.

	Control group (n=67)	Letrozole group (n=64)	P value
Age (years)	27.7±1.8	27.9±1.9	0.713
Weight (kg)	67.1±7.8	65.6±12.2	0.630
Height (cm)	161.7±2.3	161.6±7.1	0.910
BMI (kg/m <sup>2</sup> )	25.6±3.2	25.1±4.4	0.045
Infertility duration (yrs.)	5.35±1.9	5.0±3.0	0.099
<i>Infertility type</i>			
Primary%	80.6%(54)	81.25%(52)	0.835
Secondary%	19.4%(13)	18.75%(12)	0.810
Previous IUI%	55.2%(37)	50%(32)	0.638
Day 3 LH (m IU/ml)	7.3±5.6	8.2±7.86	0.613
Day 3 FSH (m IU/ml)	6.8±2.5	.8±2.2	0.181
TSH (µg/dL)	3.9±2.1	3.5±5.3	0.615
Prolactin (mg/dL)	15.4±5.8	14.3±11.2	0.835

**Table 2.** Results of conducting IUI in infertile patients who had polycystic ovarian syndrome. P values from student t-test and Chi2. BMI: Body mass index, LH: luteinizing hormone FSH: follicular stimulating hormone, TSH: Thyroid stimulating hormone.

	Control group (n:67)	Letrozole group(n:64)	P value
Premature LH surge	14.9%(10)	4.7%(3)	0.003
Pregnancy rate	8.9%(6)	21.9%(14)	0.005
Abortion rate	33.3%(2)	21.4%(3)	0.095
Ongoing pregnancy	5.9%(4)	17.2%(11)	0.005
E2*(pmol/L)	943.2±215.3	1542.3±1747.1	0.005
LH*(mIU/ml)	9.4±2.1	7.2±1.3	0.026
Number of follicles>18 mm	2.94±1.01	3.00±1.0	0.86
Endometrial thickness(mm)	8.31±1.6	9.9±1.3	<0.001

\*The day of injecting HCG.

by defect in ovulation which is as a result of hyper-secretion of LH. An important stage for a successful pregnancy is the ovulation. To have a normal ovulation, hormones such as LH, FSH, estrogen and progesterone should be secreted in a regular pattern; therefore, premature LH surge not only causes defect in ovulation, but also, it can cause defect in IUI. Thus, ovulation inducing methods should pay attention to LH reducing agents more than before [21]. CC is an anti-estrogen drug which is used as the first line therapy for such patients. Its mechanism is inducing the ovulation as well as reducing the LH serum levels. Some studies suggested that consuming CC at the end of follicular phase before using HCG can prevent premature LH surge; thus, it seems that CC can be effective in patients with PCOS who underwent IUI [8, 22]. Although it seems that CC can be effective in PCOS infertility, researchers reported about 20% resistance; moreover, like any other drug, CC can also have some complications such as ovarian overstimulation, high rate of multiple gestation, congenital anomalies, damages to cervical and endometrial mucosa and low birth weight [10, 11, 17, 21]. Thus, its effectiveness in infertility therapy was undetermined.

One choice which can be replaced by CC is Letrozole which is a specific aromatase inhibitor. This agent can induce ovulation by reducing the secretion of estrogen as well as increasing the secretion of LH in brain tissue; therefore, it can be used as a treatment for PCOS infertility. Moreover, letrozole can inhibit premature LH surge by reducing positive feedback effect in hypothalamus-hypophysis axis. While it induces some defect on endometrium and cervix because of its local effect, it also can have positive impact on maturation of endometrium and implantation [15, 16, 23, 24]. A study by Begum *et al.* demonstrated that letrozole is more effective than CC in treatment of PCOS [25]. Another study by Casper *et al.* showed that aromatase inhibitors such as letrozole can increase ovarian sensitivity to OHSS and thus, can play a role in IUI as well as treating PCOS [24]. Another study by Sedighi Maroof *et al.* suggested letrozole as a better and less expensive therapy for PCOS than ovarian drilling method [21]. However,

another study declared that these two methods were both equal in treating PCOS [26].

Fisher *et al.* compared CC and letrozole in treating PCOS in normal ovulatory women. They demonstrated that ultrasound view of endometrium and gonadotropin hormone levels in serum was all the same in both drugs; yet, estradiol levels after prescribing letrozole were more than 2 times greater than after CC consumption [15]. A few studies have assessed the effects of these two drugs on premature LH surge. In a cohort study by Branigan *et al.*, the effects of CC and oral contraceptive pills (OCP) in preventing hypersecretion of LH in women who were gone under IUI was assessed. Thirty-two patients were placed on monophasic low-dose Desogen continuously for 5-6 weeks; 100 mg CC was started on day 3 after the start of menses for 8 days. Daily ultrasound, estradiols and twice daily serum LH levels were drawn after 5 days of stimulation. HCG (10,000 IU im) was given when at least two follicles were  $\geq 16-20$  mm mean diameter and an endometrial thickness of  $\geq 7.5$  mm was present. After repeating this cycle for about 71 times, results manifested that this treatment had no significant difference by the routine one (prescribing the gonadotropins agonists); yet, reduction in secretion of LH was significantly more than the routine treatment [27].

Al-Inany *et al.* assayed the effect of CC in reducing LH secretion. Two-hundred thirty couples who were admitted by unknown origin of infertility were divided into 2 groups. From day 3 of their menses, they prescribed 75 IU human menopausal gonadotropin (HMG) for about 5 days. After 4 days, 50 mg CC was started every 3 days. Then after 5 days, TVS as well as 10000IU HCG was begun to be prescribed till the size of at least 2 follicles reached  $\geq 15$ mm. IUI was conducted after 36-48 hours. Afterwards HCG, estradiol, LH and endometrial thickness were measured. The results showed that the number of patients with premature LH surge had a significant difference than those in control group; however, the rate of pregnancy had no significant difference between the two groups [8]. Recently, letrozole was also introduced as an appropriate treatment for inhibiting premature LH surge, meanwhile, few studies can be found in



this regard. In a review article by Ziemger in 2003, it was suggested that letrozole can have a role in inhibiting premature LH surge by reducing estradiol serum levels which inhibit LH secretion at the end of follicular phase [28, 29]. In a study conducted by Bedaiwy *et al.* the effect of letrozole on hormones and endometrium thickness was evaluated. Two hundred and eight infertile women were divided into 3 groups: the first (n=47) group received nothing, for the second group (n=125) 2.5 mg Letrozole was prescribed in days 3 to 7 and the third one (n=36) was given 5 mg letrozole in days 3 to 7 of menstruation period. After reaching the size of at least 2 follicles to  $\geq 16$  mm, 10000IU of HCG was injected to all patients. TVS was conducted four times for them in days 3, 7, 9 and 11. After measuring LH, estradiol serum levels and endometrial thickness, it was concluded that letrozole can both inhibit premature LH surge and increase the rate of pregnancy in infertile patients [30]. Another survey conducted by Allegra *et al.* showed that prescribing gonadotropin releasing hormone antagonists for promoting IUI in stimulatory ovarian cycles can effectively reduce premature LH surge. Hundred and four patients were gathered in mentioned study and they were divided randomly into two groups. One group (n=52) was given recombinant FSH as well as Citreorelix (injectable gonadotropin-releasing hormone antagonist) while the other group was just given FSH. The percent of pregnancy was achieved about 53.8% in the experimental group and 30.8%

in control ones. Moreover, the serum LH level was also detected to be obviously lower in the experimental group compared with the control group [23].

### Conclusion

In conclusion, this study showed that letrozole could inhibit premature LH surge, be useful in treatment of infertility followed by polycystic ovarian syndrome (PCOS) resistant to CC and can improve the efficacy of IUI. However, small statistical population, low performance in conducting the study and differences among the individuals could all affect our results; thus, because of the importance of infertility among the society as well as economic disadvantages in conducting ineffective procedures, further studies are needed to investigate the effects of letrozole in improving the results of IUI procedures for patients with PCOS.

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### Conflict of Interest

Authors declared no conflicts of interest.

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