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The Effect of Clomiphene Citrate Versus Letrozole on Pregnancy Rate in Women With Polycystic Ovary Syndrome: A Randomized Clinical Trial

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Abstract

Objectives: Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age (6.8%-18%) and is one of the leading causes of infertility due to ovulation factors in 55%-70% of infertile women. In this study, we compared the first-line and second-line treatments of infertility through ovulation induction with clomiphene citrate and letrozole, respectively, in the infertile patients with PCOS.

Patients and Methods: This randomized clinical trial included 80 infertile patients with PCOS intent on pregnancy. Having considered the inclusion criteria and obtaining the informed consent, the patients were divided into two groups of 40 and treated with either clomiphene citrate or letrozole. In the first group, two tablets of clomiphene (50 mg/d) were taken and in the second group, two tablets of letrozole (2.5 mg/d) were prescribed on the third to seventh days of the menstrual cycle for 5 days. Over the course of the treatment for 3 months, pregnancy rate was detected at every menstrual cycle by performing BHCG titers. Data were entered into SPSS software version 21.0. All data were analyzed using independent t-test, and chi-square test with a significance level less than 0.05.

Results: Mean age of patients, and mean body mass index (BMI), as well as duration of infertility were not significantly different between letrozole and clomiphene groups. Fifteen patients in the clomiphene group (37.5%) reported a history of infertility treatment, compared to the letrozole group in which 12 patients (30%) reported such treatment, though this difference was not statistically significant. In the clomiphene group, the menstrual cycle was compatible with PCOS in 30 patients (75%), while in the group receiving letrozole, it was compatible in 33 patients (82.5%). Hyperandrogenism consistent with PCOS was present in 25 patients (62.5%) in the clomiphene group and in the group receiving letrozole in 22 patients (55%). The evidence of PCOS-compatible ultrasonography was found in 31 patients (77.5%) in the clomiphene group and in 35 patients (87.5%) in the letrozole group. The frequency of pregnancy in the clomiphene group (45%) was lower than that in the letrozole group (50%). Chi-square test showed that this difference was not statistically significant.

Conclusions: It seems that the efficacy and success rate of clomiphene and letrozole in the treatment of infertility due to ovulation failures are similar in patients with PCOS in that both could increase ovulation and pregnancy rate. In other words, these two drugs are not superior to each other and can be selected according to the patient's tolerance, cost, and side effects.

Keywords: PCOS, Clomiphene citrate, Letrozole, Ovulation induction, Infertility

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women and is the leading cause of infertility due to oligo-ovulation or anovulation (1). It affects 5%-10% of women at reproductive age according to NIH/NICHD criteria (2).

According to Rotterdam 2003 criteria, PCOS is diagnosed when at least two of the following three quantitative criteria are satisfied: the amount of menstrual bleeding (oligo menorrhea or amenorrhea), clinical or biochemical symptoms of increased male hormones, and sonographic findings suggesting polycystic ovary (3,4).

The prevalence of PCOS varies between 2.2% and 26% in different countries (5). The difference in the prevalence of PCOS is attributed to the clinical and biochemical characteristics of these patients which may differ according to race and ethnicity (6). Moreover, the prevalence of PCOS may vary with age and community. The prevalence seems to be higher in young women than those over 35 years of age (7).

PCOS is considered to be a complex trait arising from the interaction of genetic and environmental factors, usually first presenting when mature gonadotropin levels are achieved at puberty. It occurs naturally in non-human primates as well as humans. The pathogenesis of PCOS can be envisioned according to a 'two-hit" hypothesis, whereby the disorder arises as a congenitally programmed predisposition (first hit) which is made manifest in the

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presence of a provocative factor (second hit) (8).

The congenital factors can be either hereditary (genetic) or acquired (e.g., maternal drugs or nutritional disorders affecting the fetus). The postnatal provocative factor usually is insulin-resistant hyperinsulinism, which may be congenitally programmed and/or acquired postnatally due to simple (exogenous) obesity.

These complex interactions generally mimic an autosomal dominant mode of inheritance with variable penetrance. Heritability of PCOS has been estimated over 70%, based on studies in identical twin sisters (8).

Approximately 90% of individuals with PCOS have abnormal ovarian function. Abnormality in degree of insulin resistance, obesity, or luteinizing hormone (LH) excess are each found in about half of the cases. Thus, the common denominator in PCOS appear to be ovarian hyperandrogenism, with insulin-resistant hyperinsulinism being a non-essential but common aggravating factor in the pathophysiology. Moreover, LH excess and the propensity to obesity seem to be secondary to the underlying ovarian hyperandrogenism and hyperinsulinism (8,9).

Oligo-ovulation or anovulation, dysfunctional uterine bleeding, increased risk of endometrial cancer, increased risk of glucose intolerance, gestational diabetes mellitus, type 2 diabetes mellitus, and cardiovascular complications are chronic complications of PCOS. Infertility and long-term anovulation are the most known reasons for referring to gynecologist, and the cause of infertility is chronic ovulation failure. Fertility in these patients has been reduced due to a reduction in the frequency and unpredictability of ovulation, as well as the increase of abortion rates (10).

Non-medical therapies, medical treatments, and in some cases, surgery are the modalities used for treating the disease. Non-pharmacological treatments for this group include dietary restrictions and physical activity. While, medicinal treatments include the administration of contraceptive pills, medroxyprogesterone acetate, GnRH agonists (gonadotropin releasing hormone), glucocorticoids, spironolactone, and cyproterone acetate, which are prescribed by the physician according to the patients' requirements (11).

Generally, PCOS could be managed depending on the symptoms. In unplanned pregnancy in individuals with active ovary as well as being exposed to estrogen alone, abnormal uterine bleeding is seen which should be treated with progesterone to prevent endometrial cancer. If there are signs of hyperandrogenism such as acne and hirsutism, treatment should be based on these symptoms. Definitive treatment for hirsutism is electrolysis and laser, and the infertility should be treated appropriately (11,12).

Clomiphene citrate is a selective estrogen receptor regulator that antagonizes the negative feedback of estrogen in Hypothalamus, and leads to an increase in ovarian stimulation with gonadotropin; it has been used for this purpose for decades (13). Clomiphene has some drawbacks, including poor overall efficacy (only in 22% of live births with six full periods of intake), relatively high multiple pregnancy (3%-8%) compared to non-assisted pregnancy rates (<1%), and a series of undesirable effects, including changes in mood and flushing, and resistance to clomiphene (14).

In recent years, letrozole has been replaced by clomiphene as an aromatase inhibitor. Letrozel has a short half-life (about two days) and is rapidly expelled from the body. Letrozole inhibits the aromatase enzyme by inhibiting the conversion of androgen to estrogen and increasing the levels of androgens in the ovary. Letrozole administration in the follicular phase neutralizes the negative effect of estrogen on the pituitary and hypothalamus, thereby increasing the gonadotropins. Unlike clomiphene, this drug has no effect on estrogen receptors (15,16).

The potential benefits of aromatase inhibitors versus selective estrogen receptor modulators include more stimulation of endometrium, a lower multiple pregnancy rate through the use of single-follicle (17), lesser vasomotor and mood changes, and higher clearance; consequently, it decreases the probability of fertilization. However, the potential teratogenicity of letrozole remains a concern, around which many studies have been done (18).

Second-line of treatments are follicle-stimulating hormones (FSHs) and/or laparoscopic ovarian drilling.

Laparoscopic ovarian drilling is as effective as FSH treatment and results in a lower risk of higher-order gestations and ovarian hyperstimulation syndrome. However, surgery is required, and this is a major disadvantage compared with FSH injections (19).

Considering that clomiphene and letrozole are used for ovulation induction, we decided to study the effects of these two drugs on ovulation.

Patients and Methods

The present randomized clinical trial was conducted in Ali ibn Abitaleb hospital, Zahedan University of Medical Sciences, during 2016-2017 (Figure 1). The ethical code (IR.ZAUMS.REC.1395.47) was obtained from the Ethics Committee of the University and the trial was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20180602039952N2). The statistical population consisted of 80 patients aged 18-40 years old with PCOS referring to the Infertility Clinic of Hospital and were diagnosed as infertile in the context of PCOS.

The inclusion criteria were: the normalization of thyroid function tests and prolactin, having at least one healthy fallopian tube and normal uterine cavity, normalization of the patient's semen analysis, and a one-year history of infertility with respect to regular sexual intercourses (2 to 3 times per week) without contraception. Exclusion criteria were: thyroid dysfunction and high prolactin, tubal dysfunction, uterus factor, impaired semen analysis of the patient's partner and using medications such as metformin, previous history of using clomiphene or

letrozole and underlying medical problems such as renal and pulmonary diseases, diabetes, and antiphospholipid syndrome.

After obtaining informed consent, easy and accessible sampling and blocked randomization, patients were divided into two groups of 40 and were treated with letrozole or clomiphene citrate.

In the clomiphene citrate group, patients received 100 mg of clomiphene daily (two 50 mg tablets daily based on infertility literature) during the third to seventh days of the menstrual cycle for 5 days. While in the letrozole group, 5 mg (equivalent to 2 tablets of 2.5 mg based on infertility literature) were received daily for 5 days from the third to seventh days of the menstrual cycle. The patients were monitored with transvaginal ultrasound, and HCG was prescribed for LH surge if there was 1 or more than one dominant follicle with triple line endometrial pattern, HCG administration was then followed for 12 days, and serum BHCG was analyzed. This process was performed in triplicate. The data were entered into SPSS software version 21.0. All data were analyzed using Chi-square test with a significance level less than 0.05.

Data Analysis

To describe the quantitative data, the mean and standard deviation, minimum and maximum levels, and qualitative data were used from frequency and percentage. To compare the quantitative data during different time intervals and also between the two treatment groups, analysis of variance with repeated data was performed.

Data were entered into SPSS software version 21.0 after completing. All data were analyzed using independent *t* test and chi-square test with a significance level less than 0.05.

Results

In this study, 40 patients were treated with clomiphene, while 40 received letrozole. The mean ages of patients in the clomiphene and letrozole groups were 29.85 ± 6.39 and 29.92 ± 6.97 years, respectively. In addition, the mean body mass indices (BMIs) in clomiphene and letrozole groups were 24.82 ± 3.38 kg/m^2 and 25.55 ± 3.49 kg/m^2, respectively. In the end of the study, 18 patients (45%) in the clomiphene group and 20 patients (50%) in the letrozole group got pregnant. Data analysis showed no significant difference in the pregnancy rate between the 2 groups (P> 0.05).

The mean and standard deviation of the duration of infertility in the clomiphene-receiving group was 5.62 ± 3.95 years, varying at least from 2 to 15 years, compared to the mean and standard deviation of the duration of infertility in the letrozole group which was 4.07 ± 4 .77 years, varying from at least 1 to maximum 15 years. The Mann-Whitney test showed that this difference was not statistically significant (P = 0.07).

Additionally, the history of infertility in the clomiphene group was reported by 15 patients (37.5%) and in the letrozole group by 12 patients (30%). Chi-square test showed that this difference was not statistically significant (P = 0.47).

Furthermore, the menstrual cycle was consistent with PCOS in 30 patients (75%) in the clomiphene group and in 33 patients (82.5%) in the group receiving letrozole. Chi-square test showed that this difference was not statistically

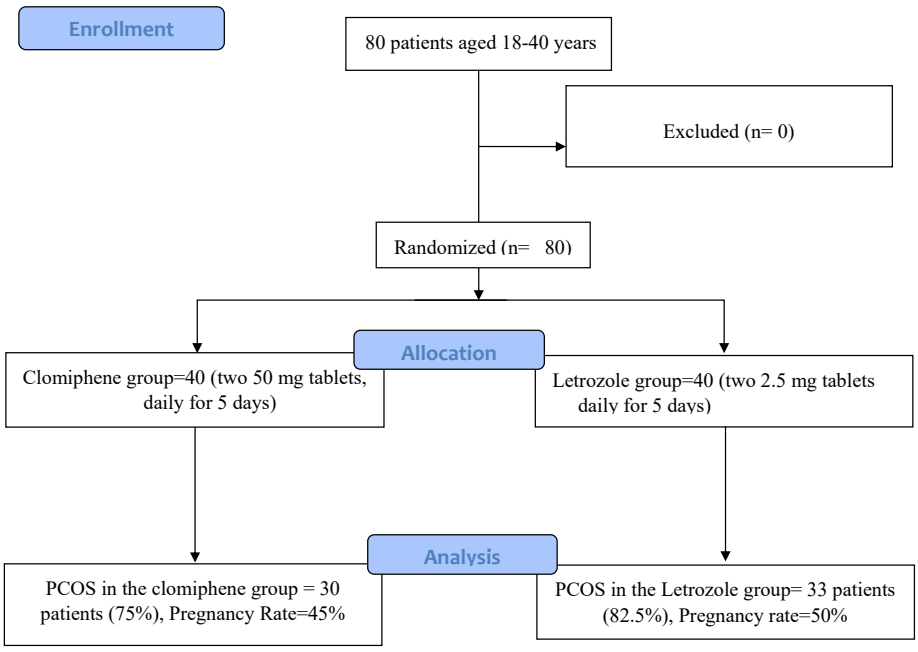

Figure 1. Flowchart of the Study.

significant ($P = 0.41$) (Table 1).

Moreover, hyperandrogenism was consistent with PCOS in 25 patients (62.5%) in the clomiphene group and in 22 patients (55%) in the group receiving letrozole. Chi-square test showed that this difference was not statistically significant ($P = 0.49$). The evidence of PCOS-compatible ultrasonography was found in 31 patients (77.5%) in the clomiphene group and in 35 patients (87.5%) in the letrozole group. This difference was not statistically significant, as determined by chi-square test ($P = 0.23$) (Table 2).

Finally, the frequency of pregnancy in the clomiphene group (45%) was lower than that in the letrozole group (50%) (Table 3).

Discussion

Ovulation induction by clomiphene citrate is usually the first treatment option for WHO-class II patients. The mechanism by which clomiphene acts is related to the negative feedback of estrogen, which causes increased gonadotropin secretion and ovulation. Although clomiphene therapy is associated with high ovulation (60%-80%), less than half of these patients will get pregnant and the frequency of ovarian hyperstimulation syndrome and multiple pregnancy will be low.

The disproportion between ovulation and pregnancy rate and the high incidence of abortion are due to the effect of clomiphene on oocyte, endometrium, and cervical secretions. The clomiphene forms for clinical treatment are 2 isomers of En clomiphene and Zu clomiphene, which are very different in terms of the biological half-life. En clomiphene is rapidly eliminated from the blood, while Zu clomiphene is excreted very rarely, and it causes unwanted side effects, and anti-estrogenic effect on the quantity and quality of cervical secretions, as well as endometrial proliferation in the next cycle.

The use of aromatase inhibitors as a novel drug for ovulation induction and for complication prevention instead of clomiphene has been considered in recent years. Letrozole is considered a third generation of these drugs, the application of which is seen in several studies (8,9). In patients with polycystic ovaries, in comparison to clomiphene, treatment with letrozole is much related to one follicle and to high endometrial thickness. As a result, letrozole could be an approvable drug for ovulation induction and can be used alone or in combination with gonadotropin in intrauterine insemination and in vitro fertilization (IVF) infertility treatments, especially in patients resistant to clomiphene as well as in cancerous patients especially those with breast and/or ovarian cancers because of not rising the serum estrogen. While clomiphene citrate, despite being commonly used for ovulation induction, is associated with a high rate of ovulation, and low pregnancy rate.

In the present study, the age of patients in 2 groups were not significantly different, since the patients were matched regarding the age before entering the study. In addition, the mean BMI was not significantly different between the 2 groups. While the duration of infertility varied between the 2 groups (from 1 to 15 years). The history of infertility was observed in 15 patients (37.5%) in the clomiphene group and in 12 (30%) patients in the letrozole group, and the PCOS-compatible cycle was seen in 30 patients (75%) in the clomiphene group and in 33 patients in the group receiving letrozole; though this difference was not statistically significant. Hyperandrogenism was consistent with PCOS in 25 patients (62.5%) in the clomiphene group and in 22 patients (55%) in the letrozole group; this difference was negligible and not significant. The evidence of PCOS-compatible ultrasonography was found in 31 patients (77.5%) in the clomiphene group and in 35 patients (87.5%) in the letrozole group. After statistical analysis, ovulation was observed in two groups. Therefore, both drugs could be used as the first line treatments by these patients.

Casper concluded that letrozole is as effective as clomiphene and requires fewer monitors due to less complications (11). The results of this study agree with those of Badawy et al (12). Jiang and He in a meta-analysis compared the letrozole with clomiphene in ovulation induction and assessed the efficacy and safety of letrozole in PCOS. In their study, letrozole was associated with less mature follicle count in each cycle. There was also no significant difference between pregnancy rate, and abortion in several cycles of intake of letrozole and

Table 1. Comparison of the Frequency of PCOS-Compatible Cycles Between the Study Groups Using Chi-Square Test

Drug	PCOS-Compatible Cycles				*P* Value
	Yes		No		
	No.	%	No.	%	
Clomiphene	30	75	10	25	0.41
Letrozole	33	82.5	7	17.5	

Table 2. Comparison of the Frequency of PCOS-compatible Ultrasound Evidence Between 2 Groups Using Chi-Square Test

Drug	PCOS-Compatible Ultrasound Evidence				*P* Value
	Yes		No		
	No.	%	No.	%	
Clomiphene	31	77.5	9	22.5	0.23
Letrozole	35	87.5	5	12.5	

Table 3. Comparison of Frequency of Pregnancy Between 2 Study Groups Using Chi-Square Test

Drug	Pregnancy				*P* Value
	Yes		No		
	No.	%	No.	%	
Clomiphene	18	45	22	55	0.65
Letrozole	20	50	20	50	

clomiphene. The authors concluded that letrozole was as effective as clomiphene in ovulation induction in PCOS patients (16).

During a prospective clinical trial, Elham et al studied dose-related manner of letrozole in patients with PCOS who were resistant to clomiphene, and concluded that it would be better to use letrozole at lower doses to prevent complications and increase the dosage based on ultrasound findings and number of follicles, anti-Mullerian hormone levels, as well as LH/FSH and estradiol levels (17).

Franik et al examined the effect of aromatase inhibitors in inducing pregnancy in PCOS patients, and found that letrozole leads to an increase in live birth and pregnancy rates compared to clomiphene. While there was observed no difference between the two drugs in terms of the ovarian structure based on the laparoscopy results (18).

Legro et al reviewed the therapeutic effect of letrozole and clomiphene on ovulation induction in women with PCOS during a multicenter, blind clinical trial. The results showed that letrozole increases the live birth and pregnancy rates among infertile women with PCOS (19).

Roque et al in a meta-analysis and systematic review compared the effects of letrozole with clomiphene in ovulation induction in women with PCOS and found that the live birth rate and pregnancy rate rose significantly in the letrozole group versus clomiphene group, but there was no significant difference in the number of abortions between the two groups. They stated that letrozole is superior to clomiphene in terms of live birth rate and pregnancy rate in PCOS women (20).

Ashrafi et al found no statistically significant difference between the study groups in terms of the effects of low dose human chorionic gonadotropin on follicular response and oocyte maturation in PCOS patients undergoing IVF cycles (21). Al-Fozan et al compared the effects of clomiphene and letrozole. There was no difference in endometrial thickness between the two groups, however the abortion rate was higher in the clomiphene group (22). Polyzos et al observed that the pregnancy rate was equal in both groups and there was no difference in terms of pregnancy with increasing the dose. Therefore, because of the cost and side effects of medication, it is better to begin with low doses for both drugs and adjust the dose based on the ovarian response (23). In addition, although the pregnancy rate reported in the letrozole group was slightly higher than that in the clomiphene group, in some cases, patients tended to use cheaper drugs due to the cost of letrozole. Based on the results of this study, these two drugs are not superior to each other and can be selected based on patient tolerance, cost, and side effects. Some studies have shown that clomiphene and metformin can be considered as the first line of treatment for infertility (24,25), although more extensive studies are required to compare the effect of metformin and letrozole with clomiphene and metformin.

Conclusions

Based on the results of this study, it can be argued that the use of letrozole with the aim of ovulation induction and successful pregnancy rate after three periods is equal to clomiphene use, however there are little differences in terms of the side effects of each drug and perinatal outcomes and live birth. Therefore, the careful selection can still be made according to a complete assessment of the patient's medical condition, economic costs, and other items.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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