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Evaluation of Pregnancy Rate in Women with Polycystic Ovary Syndrome Treated with Clomiphene Versus Letrozole

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Abstract

Introduction: 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 most common causes of infertility due to ovulation factors in 55-70% of infertile women. In this study, we compared clomiphene and letrozole in the induction of ovulation in patients with PCOS. Material & Method: This randomized clinical trial study included 80 infertile patients with PCOS. The patients were divided into two groups of 40, treated with letrozole or clomiphene citrate. In the clomiphene citrate group, two tablets 50 mg were taken daily and in the letrozole group, 2 tablets of 2.5 mg daily were prescribed on the third to seventh days of the cycle for 5 days. Results: In the clomiphene group, the cycle was compatible with PCOS in 30 patients (75%) and in the group receiving letrozole in 33 patients (82.5%). Hyperandrogenism consistent with PCOS in the clomiphene group was present in 25 patients (62.5%) 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 the letrozole group (50%).Conclusion: 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 and 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, Induction of Ovulation, Infertility.

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy in women and is the most common cause of infertility due to oligo ovulation or anovulation (Stein & Leventhal, 1935), it affects 5 to 10% of women of reproductive age according to NIH / NICHD criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

According to the latest definition in 2003 (Rotterdam Criterion), polycystic ovary syndrome has at least two criteria of three quantitative criteria: the amount of menstrual bleeding (oligo menorrhea or amenorrhea), clinical or biochemical symptoms of increased male hormones and sonographic findings suggesting polycystic ovary (Diamanti, Kandarakis & Legro, 2006).

The incidence of PCOS varies between 2.2 and 26 percent in different countries (Kauffman et al., 2002). The reasons for the difference in the prevalence of PCOS is that the clinical characteristics and biochemical characteristics of these patients may differ according to race and ethnicity (Koivunen et al., 1999). Moreover, the prevalence of PCOS may also vary with age and community. The incidence of PCOS seems to be higher in young women than those over 35 years of age (Hoffman et al., 2008).

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 one of the most common reasons for referring to gynecologist, the cause of infertility is due to chronic ovulation failure. Fertility in these patients has been reduced due to a reduction in the frequency and unpredictability of ovulation, as well as abortion rates has been increased (Beydoun et al., 2009).

Non-medical therapies, medical treatments and, in some cases, surgery, can be used to treat the disease. Non-pharmacological treatments for this group include dietary restrictions and physical activity. Medicinal treatments include contraceptive pills, medroxyprogesterone acetate, GnRH agonists (gonadotropin releasing hormone), glucocorticoids, spironolactone, cyproterone acetate, which are prescribed by the physician according to

patient requirements (Casper, 2009; Badawy, Abdel Aal & Abulatta, 2009).

Generally PCOS treatment is based on the symptoms. If pregnancy is unplanned, those who have a high degree of ovarian function and are in contact with estrogen alone, appears abnormal uterine bleeding that 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 them. Definitive treatment of hirsutism will be electrolysis and laser. For treatment of infertility, she should be treated appropriately (Casper, 2009).

Clomiphene citrate is an estrogen receptor selective regulator that antagonizes the negative feedback of estrogen in Hypothalamus, which leads to an increase in ovarian stimulation with gonadotropin, and has been used for decades for this purpose. Clomiphene has some drawbacks, including poor overall efficacy (only 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 (Jirge & Patil, 2010).

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. The administration of letrozole in the follicular phase leads to the removal of the negative feedback effect of estrogen on the pituitary and hypothalamus, thus increasing the gonadotropins. Unlike clomiphene, this drug has no effect on estrogen receptors (Kamath & George, 2011; He & Jiang, 2011).

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 (Rahmani et al., 2012), lesser vasomotor and mood changes and higher clearance, consequently, it decreases the probability of fertilization. However, the potential teratogenicity of letrozole remains a concern, and so many studies have been done in this field (Franik et al., 2014).

Kamath et al. (2011) examined letrozole and clomiphene in anovulation as first-line treatments, and their results indicated that letrozole had a confirmed and definite role for the treatment of women with treatment failure or resistance to clomiphene (Legro et al., 2015).

Jiang and He (2011), in a meta-analysis, compared the letrozole versus clomiphene to induction of ovulation and its efficacy and safety in polycystic ovarian syndrome. In their study, letrozole was associated with less mature follicle count in each cycle. There was no significant difference between pregnancy rate, abortion in several cycles of letrozole and clomiphene finally, it was concluded that letrozole is as effective as clomiphene in inducion of ovulation in PCOS patients (Polyzos et al., 2009).

Rahmani et al. (2012) during a prospective clinical trial studied dose of letrozole in patients with PCOS who were resistant to clomiphene, and eventually stated that it would be better to use letrozole at lower doses to prevent complications and increase Dosage based on ultrasound findings and number of follicles, Anti muller hormone levels, LH / FSH and estradiol (Ashrafi et al., 2011).

Franik et al. (2014) examined aromatase inhibitors in inducing pregnancy in PCOS patients, and their results included that letrozole leads to increasing in live birth and pregnancy rates compared to clomiphene. There was no difference between the two drugs in terms of the ovarian structure in laparoscopy (Al-Fozan et al., 2004).

Lergo et al. (2014) reviewed the therapeutic effect of letrozole and clomiphene on induction of ovulation in women with polycystic ovarian syndrome during a multicenter blind clinical trial, the results showed that letrozole causes in higher livebirth rat and higher pregnancy rates among infertile women with PCOS (Legro et al., 2015).

Roque et al. (2015) in a meta-analysis and systematic review compared the effects of letrozole versus clomiphene in induction of ovulation in women with polycystic ovarian syndrome and their results showed that the live birth rate and pregnancy rate were significantly higher 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 (Requena, Herrero & Landeras, 2008).

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

Material and Methods

The present study is randomized clinical trial that was conducted in Ali Abi Abitaleb Hospital of Zahedan University of Medical Sciences in 2016-2017 under the ethical code of IR.ZAUMS.REC.1395.47. The statistical population consisted of 40 patients aged 18-40 years old with polycystic ovary syndrome (PCOD) referring to infertility clinic of Hospital and were diagnosed as infertile in the context of PCOS.

The inclusion criteria included 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 intercourse (2 to 3 times Per week) without contraception. Exclusion criteria is including thyroid dysfunction and high prolactin, tubal dysfunction, uterus factor, impaired semen analysis of the patient's partner and using of medication such as metformin, the history of the using of clomiphene or letrozole in the past and underlying medical problems, such as renal and pulmonary disease, diabetes, antiphospholipid syndrome(APS).

After selecting patients and obtaining informed consent with easy and accessible Sampling and Block Randomization method, patients were divided into two groups of 40patients, and were treated with letrozole or clomiphene citrate.

In the clomiphene citrate group, patients received 100mg of clomiphene daily (two 50mg tablets daily) from Iran hormone Daru Company during the third to seventh days of the cycle for 5 days. In the letrozole group, 5 mg daily (equivalent to 2 tablets of 2.5 mg) from the Iran hormone daru company received daily for 5 days from the third to seventh days of the cycle, monitoring of these patients was with transvaginal ultrasound, HCG prescribed for LH surge if there was 1 or more than one dominant follicles with three line endometrial thickness, then 12 days following HCG administration, serum BHCG was analyzed. This study was for three periods of treatment. The data were entered into SPSS software version 21; all data were analyzed using independent t-test, chi-square test with significance level less than 0.05.

Results

In this study, 40 patients were treated with clomiphene and 40 received letrozole. The mean age of patients in the clomiphene group was 29.85 ± 6.39years old and 29.92 ± 6.97 years old in the letrozole group. Also, the mean BMI in clomiphene and letrozole groups was 24.82 ± 3.38 Kg/m2 and 25.55 ± 3.49 kg / m2, respectively. At the end of the study, 18 patients (45%) of the patients in the clomiphene group and 20 patients (50%) of the patients receiving letrozole were pregnant. Data analysis showed no significant difference in the pregnancy rate in the two groups receiving clomiphene and letrozole (P> 0.05).

The mean and standard deviation of the duration of infertility in the clomiphene recipient group was 5.62 ± 3.95 years, varying from at least 2 to 15 years. The mean and standard deviation of the duration of infertility in the letrozole group 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).

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

The cycle was consistent with PCOS in the clomiphene group in 30 patients (75%) and in the group receiving letrozole in 33 patients (82.5%). Chi-square test showed that this difference is not statistically significant (P = 0.41) (Table 1).

Hyperandrogenism was consistent with PCOS in the clomiphene group in 25 patients (62.5%) and in the group receiving letrozole in 22 patients (55%). Chi-square test showed that this difference is 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. Chi-square test showed that this difference is not statistically significant (P = 0.23) (Table 2).

The frequency of pregnancy in the clomiphene group (45%) was lower than the letrozole group (50%). Chi-square test showed that this difference was not statistically significant (P = 0.65). (Table 3)

Discussion

Induction of ovulation by clomiphen citrate treatment is usually the first treatment option for WHO-class II patients. The mechanism of clomiphene effect is related to negative feedback of estrogen, which causes increased gonadotropin secretion and ovulation. Although clomiphene therapy is associated with high ovulation (60-80%) but less than half of these patients will be pregnant and OHSS 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 form for clinical treatment includes two isomers En clomiphene (en cl) and Zu clomiphene (zucl) that 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 anti-estrogenic on the quantity and quality of cervical secretions and endometrial proliferation in the next cycle.

The use of aromatase inhibitors as a novel induction ovulation drug instead of clomiphene has been considered in recent years to prevent complications. Letrozole is a third generation of these drugs that has been considered and its application is seen in studies and articles. In patients with polycystic ovaries in comparison of clomiphene, treatment with letrozole is much related to one follicle and high endometrial thickness. As a result, letrozole is an approvable drug for induction of ovulation that can be used alone or with gonadotropin in IUI and IVF, especially in patients resistant to clomiphene as well as in cancerous patients such as breast and ovarian cancer because not rising of serum estrogen., but clomiphene citrate, despite the most commonly are used for induction of ovulation, is associated with a high rate of ovulation, low pregnancy rate. Mitwally et al (2001) stated that the cause of less pregnancy despite high ovulation in clomiphene, can be due to its inappropriate effect on the endometrium (Badawy, Abdel Aal & Abulatta, 2009). In the present study, the age of patients in the group receiving letrozole and the clomiphene group did not show a statistically significant difference, because the patients were matched to the age before entering the study. Also, the mean BMI in the two groups was not statistically significant. It should be noted that the duration of infertility varied between the two groups (from 1 to 15 years). The history of infertility in the clomiphene group was observed in 15 patients (37.5%) and in the letrozole group in 12 (30%) patients, and the PCOS-compatible cycle in the clomiphene group was 30 patients (75%), in the group receiving letrozole was 33 patients, this difference was not statistically significant. Hyperandrogenism consistent with PCOS in the clomiphene group was in 25 patients (62.5%) And in the group receiving letrozole was in 22 patients (55%), 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 group receiving letrozole.After statistical analysis, ovulation was observed in two groups of clomiphene and letrozole. Therefore, both drugs can be used as the first line treatment in these patients.

Present results is similar to study of Badawy et al. (2009). Casper et al. (2009) also stated during their study that letrozole is effective as clomiphene and it requires fewer monitors due to less complications (Diamanti, Kandarakis & Legro, 2006), but Begum (2009) showed that letrozole is more effective than clomiphene (Casper, 2009). Polyzos et al. (2009) stated that the pregnancy rate is equal in both groups and there is no difference in terms of pregnancy with increasing of dose. Therefore, because of the cost and side effects of medication, it is better to start both drugs at low doses and adjusted the dose based on the ovarian response (Ashrafi et al., 2011). Also, although the rate of pregnancy reported in the letrozole group was slightly higher than clomiphene group, there was no statistically significant difference between the results of Ashrafi et al. (2011).Alfozan et al. (2004) compared the effects of clomiphene and letrozole, there was no difference in endometrial thickness between the two groups, but the abortion rate was higher in the clomiphene group (Al-Fozan et al., 2004).

Due to the cost of letrozole, in some cases, patients tended to use cheaper drugs., 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, although more extensive studies are required to compare the effect of metformin and letrozole with clomiphene and metformin.

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

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Table 1. Comparison of the frequency of PCOS-compatible cycles in the two groups of study using chi-square test

drug	PCOS-compatible cycles				pvalue
	yes		no		
	N	%	N	%	
clomiphen	30	75	10	25	0.41
Letrozole	33	82.5	7	17.5	

Table 2. Comparison of the frequency of PCOS-compatible ultrasound evidence in two groups of patients with Chi-square test

drug	PCOS-compatible ultrasound evidence				pvalue
	yes		no		
	N	%	N	%	
clomiphen	31	77.5	9	22.5	0.23
Letrozole	35	87.5	5	12.5	

Table 3. Comparison of Pregnancy Frequency in Patients in Two Study Groups Using Chi-Square Test

P Value	Pregnancy				pvalue
	yes		no		
	N	%	N	%	
Clomiphen	18	45	22	55	0.65
Letrozole	20	50	20	50	