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Original Article

Comparison of the Effects of Letrozole and Clomiphene Citrate on Ovulation and Pregnancy Rate in Patients with Polycystic Ovary Syndrome

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Abstract

Background: For more than four decades clomiphene citrate has been the first line of the treatment for ovulatory disorders. The aim of this study was to compare the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome.

Methods: In this prospective double-blind study, 100 patients with polycystic ovary syndrome were randomized into two equal groups. The first group received letrozole, 5mg daily (per oral) and the second group received clomiphene, 100mg daily during the 3rd-7th days of the menstrual cycles. Intramuscular human chorionic gonadotropin (hCG) (10,000 IU) was administered to trigger ovulation when at least one mature follicle (≥ 18mm) was developed.

Results: Ovulation occurred in 30 patients (60%) of the letrozole group and in 16 patients (32%) of the clomiphene group, which showed a statistically significant difference (P=0.009). The mean number of follicles with diameter ≥14 mm on the day of administration of hCG was 1.06±0.95 in the letrozole group and 1.14±1.17 in the clomiphene group, which showed non-significant difference (P=0.962).

No difference was found in the endometrial thickness between the two groups. A non-significant increase in pregnancy rate was observed in the letrozole group (26% *v* 14% P=0.21).

Conclusion: Ovulation rate was higher in letrozole group and administration of letrozole was associated with a non-significant increase in pregnancy rate.
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Keywords ● Letrozole ● clomiphene citrate ● polycystic ovary syndrome ● ovulation induction

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Introduction

Polycystic ovary syndrome (PCOS) is a syndrome that is diagnosed with a specific criteria and exclusion of secondary causes of anovulation and hyperandrogenism. Current recommendation for the diagnosis of PCOS

includes two of the three criteria:[1] polycystic ovaries,[2] oligo-ovulation or anovulation, and/or,[3] clinical or biochemical evidence of hyperandrogenism.[1-3]

For more than four decades clomiphene citrate has been the first line treatment for ovulatory disorders.[3-5] Clomiphene is easy to use and results in ovulation in most patients (60%-90%), but the pregnancy rates are disappointing (10%-40%). This has been attributed to its peripheral antiestrogenic effects on the endometrium, cervical mucus, and other undetermined fertility factors.[6-12] Insulin resistance and hyperinsulinemia are common features in women with PCOS. Those patients who are resistant to clomiphene require alternative treatments. Insulin-sensitizing agents (e.g. metformin) alone or in combination with clomiphene can restore ovulation.

Gonadotropin preparations such as human menopausal gonadotropin (hMG) or pure FSH have been used as a second-line treatment for ovulation induction by some physicians.[7,9,13,14] Because of the high sensitivity of the ovaries to gonadotropin stimulation in women with PCOS, treatment with hMG or pure FSH may induce several ovulatory follicles, which may lead to multiple pregnancies and ovarian hyperstimulation syndrome.[9,15] Therefore, a simple oral treatment that could be used without risk of ovarian hyperstimulation and with minimal need to monitoring would be the preferred treatment.[9]

Aromatase inhibitors originally were developed for the treatment of breast cancer. Aromatase is a cytochrome P-450 hemoprotein that catalyzed the rate- limiting step in estrogen synthesis. That is the 3-hydroxylation step in the conversion of androstenedione and testosterone to estrone and estradiol, respectively.[3]

Anastrozole and letrozole are selective aromatase inhibitors. They are reversible and highly potent that can decrease estrogen levels by 97% - 99% by using the doses of 1 to 5 mg per day.[7] Whereas clomiphene stimulates endogenous FSH secretion by inhibition of central estrogen negative feedback via estrogen receptor antagonism, the effect of aromatase inhibitors is due to inhibition of peripheral estrogen production.[7]

Therefore, administration of an aromatase inhibitor in the early phase of the menstrual cycle results in the release of the hypothalamic/pituitary axis from estrogenic negative feedback, increasing gonadotropin secretion and resulting in stimulation of ovarian follicle development.[3,7,9,13,16,17]

In the present study, we compared the effects of letrozole and clomiphene in patients with PCOS and infertility undergoing ovulation induction.

Patients and Methods

During the period of February 2004 through November 2006, 100 patients with PCOS who attended the outpatient infertility clinics at Shiraz University of Medical Sciences participated in the present study. The study was approved by the Institutional Ethics Committee of the University. An informed written consent was obtained from each patient.

In this prospective double-blind study, 100 patients with the diagnosis of PCOS (using the Rotterdam criteria), were randomized into two equal groups. Only the pharmacist knew the name of the medication that had been taken by the patients. The first group received letrozole (Femara, Novartis pharma, AG, Basel, Switzerland) 5mg daily (per oral). The second group received clomiphene citrate (Iran Hormone Pharmaceutical Company, Tehran, Iran) 100 mg per day. Each patient underwent ovulation induction only for one menstrual cycle and took letrozole or clomiphene as the first line treatment. They had not received any other medication for ovulation induction before enrollment to the study.

The inclusion criteria were; infertility for at least one year, having patent tubes on hysterosalpingogram, and normal semen analysis of the patients' husbands. None of the women had received any hormonal or infertility therapy for at least 6 months before enrollment to the study. Both drugs were administered during the 3rd-7th days of a menstrual cycle.

Blood samples for the measurement of FSH, LH, testosterone, dehydroepiandrostendione sulfate (DHEAS), prolactin and TSH levels were obtained on day 3 of spontaneous or withdrawal cycle.

Transvaginal ultrasound examination were performed prior to starting the treatment on day 3 of the cycle, day 10-12 of the cycle, and more often as needed with a 5-MHZ vaginal transducer attached to a Aloko Scanner (Model SSD-500, Aloka Co, LTd, Tokyo, Japan).

Follicular diameter was determined by calculating the mean of two perpendicular diameters measured at the largest plane of the follicle. Intramuscular hCG (Profasi®, Serono factory, Swiss or Pregnyl®, Organon factory, Nederland) at the dose of 10,000 IU administered to trigger ovulation when at least one mature follicle (≥18mm) was developed followed by timed intercourse.

The endometrial thickness was measured at the greatest diameter perpendicular to the

midsagital plane in the fundal region, including both layers of the endometrial thickness.

Blood samples for the measurement of progesterone levels were obtained on days 21-23 of menstrual cycles. Level ≥ 3 ng/ml was considered as a marker for ovulation.

Serum β-hCG was measured 5 days after a missed period. The pregnancy rate was calculated on the basis of a positive result of a serum β-hCG level >10mIU/ml. Ultrasound was performed 2 to 4 weeks after a positive pregnancy test to confirm clinical pregnancy by fetal cardiac activity and number of gestational sacs. The follow-up continued from clinical pregnancy confirmation by ultrasonography until delivery or pregnancy loss.

Total number of follicles with diameter ≥14 mm and endometrial thickness on the day of hCG injection, ovulatory rate, pregnancy rate, miscarriage rate, and rate of multiple pregnancy in both groups were evaluated.

Statistical Analysis

The analysis was done by using SPSS version 11.5. Statistical analysis was performed using two sample *t* test, Mann-Whitney U test, and Fisher's exact test. P value <0.05 was considered as statistically significant. Results were expressed as means ± SD.

Results

The two groups were similar regarding the demographic characteristics, including age, body mass index (BMI), duration of infertility, PCOS phenotypes and basal serum levels of FSH, LH, testosterone, DHEAS, prolactin, and TSH (table 1).

Ovulation occurred in 30 patients (60%) of letrozole group and in 16 patients (32%) of clomiphene group, which showed a statistically significant difference (P=0.009).

Mean number of follicles with diameter ≥14mm on the day of hCG administration were similar in both groups (P=0.96, table 2). The mean endometrial thickness on the day of hCG administration in letrozole and clomiphene groups showed no statistically significant difference (P=0.16, table 2).

Pregnancy was occurred in 13 patients (26%) of the letrozole group and in 7 patients (14%) of the clomiphene group, which was not statistically significant (P=0.21, table 2). Of them three patients (23%) in the letrozole group and one patient (14.3%) in clomiphene group had abortion, which was not significantly different (P=1). The remaining pregnancies reached term. One twin pregnancy was occurred in either group [7.7% in letrozole group *v* 14.3% in clomiphene group which was not significantly different] (P=1).

We did not find any major congenital anomaly in letrozole group, however, one major congenital anomaly was detected in clomiphene group (meningomyelocele). No minor anomalies were observed in both groups.

Discussion

PCOS is characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries.[1-3]

Table 1: Demographic characteristics of the patients treated with letrozole and clomiphene.

Variable	Letrozole group (n=50)	Clomiphene group (n=50)	95% CI	P value
Age (Years)	23.62±2.92	24.32±3.43	-1.96 to 0.56	0.27
BMI (Kg/m^2)	27.45±4.61	27.09±3.61	-1.28 to 1.99	0.66
Duration of infertility (Years)	2.00±1.34	2.30±1.85	-0.94 to 0.34	0.61
Oligomenorrhea	49(98.00%)	47(94.00%)	-0.04 to 0.08	0.61
Polycystic ovary	49(98.00%)	46(92.00%)	-0.04 to 0.10	0.36
Hirsutism	18(36.00%)	25(50.00%)	-0.09 to 0.24	0.23
FSH (mIU/ml)	5.87±3.11	5.83±2.28	-1.05 to 1.12	0.94
LH (mIU/ml)	9.31±5.76	12.86±9.41	-6.65 to -0.44	0.08
Prolactin (ng/ml)	14.34±5.06	14.58±5.45	-2.32 to 1.85	0.82
TSH (mIU/ml)	2.36±1.18	2.33±1.27	-0.46 to 0.51	0.91
Testosterone(ng/ml)	0.60±0.19	0.85±1.64	-0.72 to 0.21	0.28
DHEAS (µg/ml)	3.53±1.71	3.80±2.29	-1.08 to 0.52	0.49

Table 2: The outcome of ovulation induction with letrozole and clomiphene.

Variable	Letrozole group (n=50)	Clomiphene group (n=50)	95% CI	P value
Total number of follicles with diameter ≥14 mm	1.06±0.95	1.14±1.17	-0.50 to 0.34	0.96
Endometrial thickness (mm) on the day of hCG injection	6.44±1.68	7.12±2.01	-1.41 to 0.05	0.16
Ovulation rate [number (%)]	30(60%)	16(32%)	0.09 to 0.47	0.009
Pregnancy rate [number (%)]	13(26.0%)	7(14.0%)	-0.04 to 0.28	0.21
Multiple pregnancy	1(7.69%)	1(14.28%)	-0.36 to 0.23	1
Abortion	3(23%)	1(14.28%)	-0.26 to 0.43	1
Delivery rate	10(76.92%)	6(85.71%)	-0.43 to 0.26	0.91

Although considerable progress has been made toward a better understanding of the pathogenesis of this syndrome, the exact cause (or causes) still is unknown.[1,2]

For the first time Mitwally and Casper reported the use of letrozole in 12 patients with PCOS; ovulation occurred in 9 of the patients (75%), and pregnancy was occurred in three patients (25%).[9]

A prospective, randomized controlled trial assessed clomiphene versus letrozole for ovulation induction in 49 women with unexplained infertility who were undergoing intrauterine insemination. The patients were randomized to receive either 100 mg of clomiphene or 2.5 mg of letrozole for 5 days starting from day 3 of menstrual cycle. Ovulation was triggered by hCG (10,000 IU/intramuscular) when the diameter of dominant follicle reached 18 mm followed by performing intrauterine insemination (IUI) 24 and 48 hours later. On the day of hCG administration, the patients in the clomiphene group had higher estradiol levels (2322.5 *v* 65 pmol/ml, P<0.0001), more follicles 14 mm in the mean diameter (2 *v* 1 P=0.005), a thinner endometrium (6.9 mm *v* 8.6 mm P=0.03), and an increased uterine artery pulsatility index (3.6 *v* 3.1 P=0.0005). A non-significant increase in pregnancy rate was observed in patients receiving the letrozole treatment (16.7% *v* 5.6% per patient, P=0.55).[18]

In another study Haya Al-Fezan, et al. compared the effect of letrozole with clomiphene in women undergoing superovulation. These authors studied total 238 cycles of superovulation and IUI in women with idiopathic infertility. Patients were randomized to receive 7.5 mg of letrozole or 100 mg of clomiphene daily. There was no significant difference between the total number of developing follicles in the letrozole (5.7±3.7) and in the clomiphene groups (4.8±2.3). No difference was found in the endometrial thickness between the two groups (7.1±0.2 mm in the letrozole group, 8.2±5.9 mm in the clomiphene group). The pregnancy rate per cycle was 11.5% in the letrozole group and 8.9% in the clomiphene group (similar pregnancy rate). Miscarriage rate in clomiphene group was 36.6% but no miscarriage was found in the letrozole group.[18]

Addition of aromatase inhibitors to gonadotropins in controlled ovarian stimulation decrease gonadotropin requirements without negative effect on pregnancy rate.[12,15,19-23]

Aromatase inhibition also improves ovarian response to follicle-stimulating hormone in poor responders. In an observational cohort study, 12 patients with unexplained infertility and a poor response to ovarian stimulation with FSH in at least two prior cycles were given letrozole, 2.5 mg daily from day 3-7 of the menstrual cycle and FSH (50-225 IU per day) starting on day 7. These women were undergoing controlled ovarian hyperstimulation for intrauterine insemination. Improved response to FSH stimulation with letrozole co-treatment was shown by the significantly lower FSH dose (616±454 IU in letrozole plus FSH cycles *v* 1590±708 IU in FSH only cycles) associated with significantly higher number of mature follicles (3.3 *v* 1.9 follicles). Three clinical pregnancies demonstrated in the letrozole plus FSH cycles.[12] Similarly, other studies have suggested the value of aromatase inhibitors in poor responders.[24-26]

In our study, the number of follicles with diameter ≥14 mm on the day of hCG injection were the same in both groups. This is consistent with a report,[13] and in contrast with another study that showed more mature follicles and thinner endometrium in clomiphene group.[18]

Endometrial thickness on the day of hCG injection were comparable in our groups similar to some reports,[3,13,19] and in contrast with others, which showed a higher endometrial thickness in those received letrozole.[9,18,20,21] We previously found that endometrial thickness at the time of hCG injection is thinner in clomiphene cycles compared with natural cycle.[11] In the present study, starting clomiphene earlier in the follicular phase (day 3-7) overcame its antiestrogenic effect on the endometrium. In addition higher level of E2 at the clomiphene cycle compared with natural and letrozole cycles, compensated the unwanted effect of clomiphene on the endometrium.[27]

In the present study, ovulatory rate was 60% in letrozole group and 32% in clomiphene group that was a statistically significant difference (P=0.009). Bayar's study showed the same ovulatory rate in both groups.[3]

Pregnancy rate was not significantly different in the present study between the two groups (26% in letrozole group *v* 14% in clomiphene group; P=0.21), however, we found a non-significant increase in pregnancy rate similar to Tulandi's study.[18] In most studies, pregnancy rate has been similar in both groups.[3,13,19-21]

In the present study, pregnancy loss was not significantly different in the both groups (23% in letrozole *v* 14.3% in clomiphene). This finding is similar with Mitwally's study that showed similar miscarriage rate in letrozole group compared with all other groups receiving current ovarian stimulation protocols.[16] One report showed higher miscarriage rate with clomiphene.[13]

Letrozole use has been associated with a significantly lower rate of multiple pregnancies compared with clomiphene in some studies.[16]

In the present study, the rate of multiple gestation was similar between two groups.

No major anomaly was found in letrozole group. One major congenital anomaly observed in clomiphene group (meningomyelocele). No minor anomalies were found in either group.

Concern about the effects of letrozole on the fetus was raised in an abstract presented at the 2005 American Society for Reproductive Medicine Meeting.[28] The authors reported the outcome of 170 infants of whom 20 were lost during follow-up. As a result, 150 newborns from 130 pregnancies were compared with a control group of over 36000 infants born from low risk pregnant women in a community hospital. The authors reported that the incidence of cardiac and bone anomalies were higher in the letrozole group than in the control group.[28]

Tulandi et al. performed a retrospective study to compare the incidence of congenital malformations in 911 newborns from women who conceived following treatment with letrozole or clomiphene and did not find a statistically significant difference.[29] Congenital malformations were diagnosed in 14/514 (2.4%) newborns in the letrozole group versus 19/397 (4.8%) newborns in the clomiphene group. The rates of major malformations were 6/514 (1.2%) and 12/397 (3%), respectively. These differences were not statistically significant.

However, there was a seven fold increase in overall cardiac anomalies in clomiphene group compared with the letrozole treated group (P=0.02). The authors concluded that letrozole had not teratogenic effect based on their data.[29]

Safety studies have not shown teratogenic or clastogenic effects in animal embryo development from exposure to anastrozole, however, there have been some concerns regarding teratogenic effect of letrozole.[30]

The approximate half-life of letrozole is 45 hours (range 30-60 hours), which is shorter than the half-life of clomiphene (5-7 days).[7,22] Letrozole should be cleared from the body completely by the time of embryo implantation. Thus, the exposure with the drug predates the critical fetal developmental period.[29]

Based on the half-life of letrozole and anastrozole, administration in the early follicular phase should result in clearance of the agents before implantation takes place.

Nevertheless, care should be taken in all cases of ovulation induction with these drugs to ensure that the patient is not pregnant. It is prudent for patients receiving an aromatase inhibitor for ovulation induction to have βhCG measurement or a progestin withdrawal bleeding before treatment to rule out early pregnancy.[31]

Casper turned his attention to anastrozole, an aromatase inhibitor with pharmacokinetic properties similar to letrozole and slightly different chemical structure that has not been demonstrated to be associated with any teratogenic, mutagenic, or clastogenic activity in vivo or in vitro.[31] Single-dose administration of this compound would also result in more rapid clearance compared with daily administration for 5 days.

In conclusion, the present study found that ovulatory rate is higher with letrozole compared with clomiphene. A non-significant increase in pregnancy rate was observed in letrozole group. Miscarriage rate and multiple pregnancy rates were comparable in both groups.

Aromatase inhibitors are effective for ovulation induction or augmentation of ovulation. And administration of them in early follicular phase could be safe for ovulation induction. Potential advantages of letrozole include reduced multiple pregnancies, absence of antiestrogenic adverse effects, and the subsequent need for less intensive monitoring. Therefore, it seems reasonable to use a treatment that is equally effective in induction of ovulation but without antiestrogenic adverse effects as a first-line therapy.

Conflict of Interest: None declared

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