Original Article

Letrozole as the first-line treatment of infertile women with poly cystic ovarian syndrome (PCOS) compared with clomiphene citrate: A clinical trial

Ataollah Ghahiri, Neda Mogharehabed, Mahboobeh Mamourian

Department of Gynecology and Obstetrics, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The purpose of this study was to determine the efficacy and safety of letrozole on ovulation induction and pregnancy in comparison with clomiphene citrate in PCOS patients.

Materials and Methods: The study was based on prospective randomized clinical trial comparing the efficacy of letrozole as the first-line management of the PCOS patients in comparison to clomiphene citrate during 2009 to 2011 and was performed in one private infertility clinic. The study included 100 patients divided into 2 equal groups.

Results: Pregnancy occurred in 29 of 50 patients in letrozole group (58%) and 24 of 51 patients in clomiphene group (47%). The difference was not statistically significant (*P* value = 0.23). Thirty patients in clomiphene group and 36 patients in letrozole group showed regular menses after or during the treatment course. No significant difference between the 2 groups was observed (*P* value = 0.21).

Conclusion: Our findings suggest letrozole and clomiphene citrate are equally effective for induction of ovulation and achieving pregnancy in patients with PCOS.

Key Words: Clomiphene, letrozole, PCOS

Address for correspondence:
Dr. Neda Mogharehabed, Department of Gynecology and Obstetrics, Al Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: nedamogharehabed@gmail.com

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INTRODUCTION

Poly cystic ovary syndrome (PCOS), characterized by ovulatory dysfunction and hyperandrogenism, is the most common cause of infertility in women.[1] The diagnosis of PCOS has life-long implications with increased risk for infertility, metabolic syndrome, type 2 diabetes mellitus, and possibly cardiovascular disease. It should be considered in any adolescent girl with hirsutism, persistent acne, menstrual irregularity, or obesity. Approximately two-thirds of patients with PCOS, whether adolescent or adult, have anovulatory symptoms.[2,3]

Clomiphene citrate (CC) is the most commonly used pharmacologic agent to induce ovulation in these women, but some women fail to conceive with this therapy. During the past decade, both insulin sensitizers, such as metformin, and aromatase inhibitors, have been used for ovulation induction in women who fail to conceive with CC. Aromatase inhibitors are a class of drugs that block estrogen biosynthesis, thereby reducing negative estrogenic feedback at the pituitary.[4]

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Unwanted anti-esterogenic features of this agent on endometrium and cervical mucus, Ovulatory Hyper Stimulation Syndrome (OHSS), and multi fetal pregnancy have forced investigators to look forward another drug with minor side-effects and acceptable efficacy. Letrozole is an aromatase inhibitor with less anti-esterogenic properties. In addition, there is no need for closed monitoring during therapy with letrozole.

The present prospective clinical trial study is an attempt to compare and determine clinical outcomes of letrozole to that of clomiphene citrate in patients with infertility due to poly cystic ovarian syndrome.

MATERIALS AND METHODS

This was a randomized prospective clinical trial, including consecutive women with primary or secondary infertility due to PCOS from Jan 2009 to Sept 2011, performed in one private infertility clinic.

The major criteria for diagnosis of PCOS were oligo- and/or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries which is in accord with the revised 2003 Rotterdam criteria of PCOS. Thyroid function, prolactin level, and husband's sperm analysis were checked for normal values.

Patients with other causes of infertility, infertility less than one year, and those who got previous treatment(s) for infertility were not included in the study.

The protocol was approved by the ethical investigation committee of our institution, and informed consent was obtained from all the patients after full informative session. All patients were visited and followed by a single physician.

Based on our statistical data, the fair needed number for performing this study was 50 per group (The sample size was calculated by considering z, p, and d as 1.96, 0.15, and 0.1, respectively). All candidates were randomized based on envelope method into either clomiphene citrate group (group A, $n = 51$) or letrozole group (group B, $n = 50$) [Figure 1].

The patients in the clomiphene group (Group A) received clomiphene citrate 100 mg for 5 days starting from day 3 of their menstrual cycle. In letrozole group, 5 mg letrozole was given for 5 days from day 3 of their menstrual cycle (Group B). Patients were advised to have intercourse in days 11, 13, and 15 of their menstrual cycles in both groups.

In order to confirm ovulation, calendar, history-taking and pregnancy occurring was used. Regular

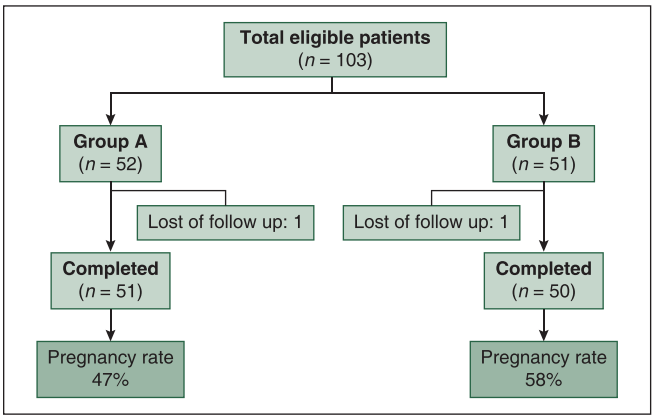

Figure 1: The chart shows the study design. Group A: Clomiphene group, Group B: Letrozole group

menstruation with dysmenorrheal considered as normal ovulatory cycles also. In case of delayed menstruation in a patient who had ovulated, β-HCG was measured, and pregnancy was confirmed and followed up to 3 months to find possible abortion or ectopic pregnancy. In case of pregnancy failure, the patients were advised to continue treatment and to participate in up to 4 courses of therapy. All data was collected by one physician and by using questionnaire. The data was analyzed by SPSS ver. 14 using chi-square, Mann Whitney, and t tests. *P* values less than 0.05 were considered significant.

RESULTS

Of the 101 women starting the program, all completed the study. One patient in group A and one patient in group B did not present again, and their pregnancy outcome remained unclear.

Baseline characteristics of patients included in the study are shown in Table 1. Mean age ± standard deviation was 25.63 ± 4.41 yr; 94.1% and 5.1% presented with primary and secondary infertility, respectively. There were no statistically significant differences between the 2 groups with regard to age, type, and duration of infertility [Table 1].

Pregnancy occurred in 29 of 50 patients in the letrozole group (58%) and 24 of 51 patients (47%) in the clomiphene group; the differences were not statistically significant (*P* value= 0.23). Thirty patients in group A and 36 patients in group B showed regular menses during the treatment course. As depicted in table 1, there was no significant difference between 2 groups (*P* value = 0.21). Frequencies of more than 3 months pregnancy in clomiphene and letrozole groups were 65% and 71%, respectively, with no statistically significant difference. Miscarriage (abortion) occurred in 5 of letrozole and 5 of clomiphene patients; the

Table 1: Patient demographic characteristics

Variables		Clomiphene (A)	Letrozole (B)	*P* value
Number of patients		51	50	–
Mean BMI ± standard deviation		27.13±4.9	28.24±5.2	0.41
Duration of infertility	1 year	4 (8%)	6 (12%)	0.48
	More than 1 year	47 (92%)	44 (88%)	
Menstrual period before therapy	Regular	–	–	NS
	Oligomenorrhea	51 (100%)	50 (100%)	
	Amenorrhea	–	–	
Menstrual period after therapy	Regular	30	36	0.21
	Still oligo-	21	14	
Pregnancy		24	29	0.23
Pregnancy more than 3 months/ pregnancies		15/24	20/29	0.50
Abortion/ pregnancies		6/24	5/29	0.38
Ectopic Pregnancy/ pregnancies		2/24	3/29	1
Mean Number of Treatment Cycles to Achieve Pregnancy ± standard deviation		2.06±0.95	1.94±0.98	0.47

difference between the groups was not statistically significant. Prevalence of ectopic pregnancies showed no significant difference between clomiphene group and letrozole group.

Twin pregnancies occurred neither in the CC group nor in the letrozole group. No higher order pregnancies or cases of ovarian hyperstimulation syndrome occurred in either group.

DISCUSSION

This trial was conducted in order to establish a simple and safe method for an ideal treatment for infertility due to poly cystic ovarian disease in Iran. Our study showed that frequency of normal ovulatory cycles and pregnancy rate were similar in both clomiphene and letrozole groups.

In the present study, no statistically significant difference was observed regarding ovulation or pregnancy rates between the 2 groups. Ovulation occurred in 30/51 (58.8%) in group A and 36/50 (72%) in group B, which is comparable to that reported recently by Badawy *et al.*[5] who had an ovulatory rate of 62% for letrozole cycles. In another trial, Mitwally and Casper[6] had ovulatory rate of 75%, Al- Omari *et al.*[7] had an ovulatory rate of 87.5%, whereas Elnashar *et al.*[8] reported an ovulation rate of 54.6%. This may be explained by the small sample size in present study. Pregnancy was achieved in 53% in group A and 58% in group B, which is not comparable to 12.2% reported by Badawy *et al.* for letrozole;[5] the miscarriage rate was similar in both of our groups.

Another study showed no statistically significant difference in the pre-treatment endometrial thickness between patients who were treated with clomiphene in contrast with patients treated by letrozole.[9]

The high estrogen level from multiple follicular growths might compensate for the alleged anti-estrogenic effect of CC on the endometrium, but there is little to no compelling evidence to support this idea. Limited endometrial proliferation has been observed in some CC-treated patients,[10] but the effect is minor or not at all evident in the large majority of women.[11-13] Although some studies have suggested that fecundity may relate to endometrial thickness, others have failed to demonstrate any significant correlation. Indeed, CC has been shown to inhibit steroid hormone production by cultured avian, ovine,[14] and human granulosa/ luteal cells,[15] but estrogen and progesterone levels in CC-induced cycles are typically significantly higher, not lower, than in spontaneous cycles. Adverse effects of CC on mouse ovum fertilization and embryo development have been demonstrated *in vitro*,[16] but circulating levels of CC never reach the concentrations required to produce these effects, even after several consecutive treatment cycles.[17] Taken together, the available evidence and accumulated clinical experience suggest that any adverse anti-estrogenic effects of CC present no major obstacle in the majority of treated women, as found in our study.

In conclusion, our findings do not show any advantages to the use of letrozole over clomiphene citrate for inducting pregnancy as a fist-line treatment in woman with PCOS, but suggest that letrozole and clomiphene citrate are equally effective for inducing ovulation and achieving pregnancy in patients with PCOS.

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