

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

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## 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

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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.<sup>[1]</sup> 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.<sup>[2,3]</sup>

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.<sup>[4]</sup>

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Unwanted anti-estrogenic features of this agent on endometrium and cervical mucus, Ovarian 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-estrogenic 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 polycystic 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.

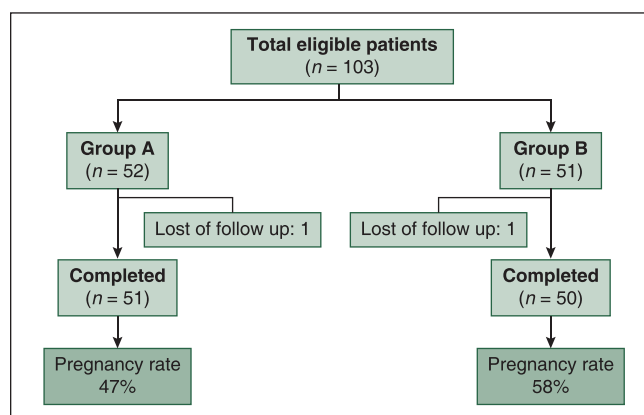
Patients with other causes of infertility, infertility less than one year, and those who got previous treatment(s) for infertility were not included in the study.

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,  $\beta$ -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  $\pm$  standard deviation was  $25.63 \pm 4.41$  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 polycystic 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.*<sup>[5]</sup> who had an ovulatory rate of 62% for letrozole cycles. In another trial, Mitwally and Casper<sup>[6]</sup> had ovulatory rate of 75%, Al- Omari *et al.*<sup>[7]</sup> had an ovulatory rate of 87.5%, whereas Elnashar *et al.*<sup>[8]</sup> 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;<sup>[5]</sup> 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.<sup>[9]</sup>

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,<sup>[10]</sup> but the effect is minor or not at all evident in the large majority of women.<sup>[11-13]</sup> 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,<sup>[14]</sup> and human granulosa/luteal cells,<sup>[15]</sup> 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*,<sup>[16]</sup> but circulating levels of CC never reach the concentrations required to produce these effects, even after several consecutive treatment cycles.<sup>[17]</sup> 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 inducing pregnancy as a first-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.

## REFERENCES

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;89:2745-9.
2. King J. Polycystic ovary syndrome. *J Midwifery Womens Health* 2006;51:415-22.

3. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41.
4. Misso ML, Wong JL, Teede HJ, Hart R, Rombauts L, Melder AM, *et al.* Aromatase inhibitors for PCOS: A systematic review and meta-analysis. *Hum Reprod Update* 2012;18:301-12.
5. Badawy A, Abdel Aal I, Abulatta M. Anastrozole or letrozole for ovulation induction in clomiphene resistant women with polycystic ovarian syndrome: A prospective randomized trial. *Fertil Steril* 2008;89:1209-12.
6. Mitwally FM, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertil Steril* 2001;75:305-9.
7. Al-Omari WR, Sulaiman W, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. *Int J Gynecol Obstet* 2004;85:289-91.
8. Elnashar A, Fouad H, Eldosoky M, Saeid N. Letrozole induction of ovulation in women with clomiphene citrate resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/ follicle- stimulating hormone ratio. *Fertil Steril* 2006;85:511-3.
9. Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: A prospective randomized trial. *Fertil Steril* 2009;92:1355-9.
10. Mahani IM, Afnan M. The pregnancy rates with intrauterine insemination (IUI) in superovulated cycles employing different protocols (clomiphene citrate (CC), human menopausal gonadotropin (HMG) and HMG+CC) and in natural ovulatory cycle. *J Pak Med Assoc* 2004;54:503-5.
11. Eden JA, Place J, Carter GD, Jones J, Alaghband-Zadeh J, Pawson ME. The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. *Obstet Gynecol* 1989;73:187-90.
12. Randall JM, Templeton A. Transvaginal sonographic assessment of follicular and endometrial growth in spontaneous and clomiphene citrate cycles. *Fertil Steril* 1991;56:208-12.
13. Sgarlata CS, Mikhail G, Hertelendy F. Clomiphene and tamoxifen inhibit progesterone synthesis in granulosa cells: Comparison with estradiol. *Endocrinology* 1984;114:2032-8.
14. Niswender GD, Davis TL, Griffith RJ, Bogan RL, Monser K, Bott RC, *et al.* Judge, jury and executioner: The auto-regulation of luteal function. *Soc Reprod Fertil Suppl* 2007;64:191-206.
15. Olsson JH, Nilsson L, Hillensjo T. Effect of clomiphene isomers on progesterin synthesis in cultured human granulosa cells. *Hum Reprod* 1987;2:463-8.
16. Schmidt GE, Kim MH, Mansour R, Torello L, Friedman CI. The effects of enclomiphene and zuclomiphene citrates on mouse embryos fertilized *in vitro* and *in vivo*. *Am J Obstet Gynecol* 1986;154:727-36.
17. Young SL, Opsahl MS, Fritz MA. Serum concentrations of enclomiphene and zuclomiphene across consecutive cycles of clomiphene citrate therapy in anovulatory infertile women. *Fertil Steril* 1999;71:639-44.

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