ORIGINAL STUDY

Letrozole for Induction of Ovulation in PCOS Patients: Resistant to Clomiphene Citrate

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Abstract

Objective: To assess the efficacy of aromatase inhibitor letrozole for induction of ovulation in anovulatory polycystic ovary syndrome (PCOS) patients in whom clomiphene citrate (CC) treatment was unsuccessful.

Design: Prospective, nonrandomized, interventional, crossover trial, using anovulatory PCOS infertile patients previously treated with clomiphene citrate as their own historic controls.

Setting: Center for Assisted Reproduction (CARE), Department of Obstetrics and Gynecology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh.

Patients: 60 anovulatory PCOS infertile patients who received 150 mg of clomiphene citrate for at least 4 cycles on days 2 to 6 of the cycle with an unsatisfactory outcome (No mature follicle and/or endometrial thickness of equal or less than 0.7 cm) were the target population.

Intervention: 5.0 to 7.5 mg of letrozole was given orally on days 2 to 6 of the cycle.

Main outcome measures: Number and size of mature follicles, endometrial thickness and occurrence of ovulation.

Results: There was a statistically significant increase in the follicular size and endometrial thickness after the administration of letrozole. Ovulation occurred in 38 patients (63.33%) in the letrozole treated cycles. Most of developed follicles (68.42%-26 patients) were multiple and majority patients (63.16%) responded to the higher 7.5 mg dose.

Conclusion: Oral administration of letrozole is an effective agent for ovulation induction in clomiphene citrate resistant PCOS patients.

Keywords: PCOS, clomiphene citrate, letrozole.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine metabolic disorder affecting 5 to 10% women of reproductive age and accounts for 80% of cases of anovulatory infertility.[1] Anovulation in PCOS is one of the most common causes for reproductive difficulty in otherwise fertile couples. Once successful ovulation is achieved, fertility is often restored in PCOS patients. At present, the two main medications used for induction of ovulation include an oral antiestrogen, such as clomiphene citrate (CC), and an injectable gonadotropins, predominantly recombinant follicle stimulating hormone (FSH).[1] Both CC and gonadotropins are associated with various disadvantages that include risk of life-threatening ovarian hyperstimulation syndrome, high order multiple pregnancy, lower pregnancy rate despite high ovulatory rate (especially for CC) and high expenses with parenteral administration requiring intensive monitoring (especially with FSH treatment).[2]

CC is the most commonly used drug for the induction and augmentation of ovulation in PCOS. However, 20 to 25% patients with PCOS are resistant to CC[3] and fail to develop follicles of desired size.[4] In addition, clinical data reveal a discrepancy between ovulation and conception rates between CC treatment, and a higher than expected incidence of miscarriage in conception cycles. These observations have been attributed to the peripheral antiestrogenic mechanism of action of CC that involves long lasting estrogen receptor depletion in the endometrium and cervix.[2,3]

Letrozole belongs to a new group of very potent, non-steroidal, selective reversible third generation aromatase inhibitor developed for postmenopausal breast cancer therapy. Letrozole generally mimics the action of CC without depletion of estrogen receptors when administered early in the menstrual cycle.[2] Because of the much shorter life span (45 hours) and absence of estrogen receptor binding, it possibly avoids the antiestrogenic effects associated with CC.[2,3,5,16-18]

In anovulatory PCOS patients, CC is usually the first choice of drug for induction of ovulation.[13,19] In CC failures, expensive gonadotropin injections (which are very difficult to afford for most of the patients in Bangladesh) are the next treatment option but, especially in PCOS, are associated with increased risk of ovarian hyperstimulation requiring intensive monitoring (which again adds to the cost).[22] The other option in PCOS is the invasive and relatively expensive laparoscopic ovarian drilling procedure with facilities mainly confined to limited centers in Bangladesh. So, obviously a cheap oral agent is preferred in our context that can induce ovulation in resistant PCOS cases without extensive monitoring and surgical intervention and having fewer side effects on the endometrium.[14] This prospective interventional study has therefore been carried out to assess the efficacy of letrozole for induction of ovulation in clomiphene resistant anovulatory PCOS patients.[15]

MATERIAL AND METHODS

This study was conducted at the center for assisted reproduction (CARE), BIRDEM in between August 2007 to December 2008. Polycystic ovary syndrome (PCOS) patients were diagnosed using the Rotterdam ESHRE/ASRM-consensus workshop group, 2004 criteria. (Presence of two out of three criteria- (i) oligo and/or anovulation; (ii) clinical and/or biochemical signs of hyperendrogenism and (iii) echographic polycystic ovary). Sixty (60) anovulatory PCOS patients were then selected all of whom were previously treated with 150 mg of clomiphene citrate for at least 4 cycles with an inadequate outcome (no mature follicle and/or endometrial thickness of equal or less than 0.7 cm). PCOS patients with abnormal serum testosterone level/ abnormal prolactin level/ abnormal thyroid function tests, associated male factor infertility, suspected tubal factor infertility, unexplained infertility and patients receiving recombinant FSH along with letrozole were excluded from the study.

At least one-month interval was given to avoid any residual effect of clomiphene citrate. Informed consent was taken from the patients following whom 5.0 mg of letrozole was given orally on days 2 to 6 of the cycle. Patients were followed-up on D13/ D14 by transvaginal sonography (TVS). The number and size of mature follicles and endometrial thickness were assessed. In this center, criterion set for successful induction include diameter of at least 21 mm in case of one mature follicle or 17 mm in case of multiple follicular development. Endometrial thickness of 8 mm or more was considered as a satisfactory response. Patients who failed to respond to 5 mg dose eventually received 7.5 mg of letrozole in the next cycle. Patients with an inadequate response to 7.5 mg dose for two (2) consecutive cycles were labeled as failure.

Patients who successfully developed mature follicles according to the above criterion received 5000 units of hCG. A repeat TVS was done 48 to 72 hours after the injection of hCG and ovulation was determined by observing the rupture of follicle. A paired t-test was done to ascertain the level of significance and a P value of < 0.05 was considered significant.

RESULTS

Age of the patients in this study ranged between 24 to 40 years with a mean of 31.31 years. BMI (kg/m^2) ranged from 23 to 32 with an average of 27.5. The average duration of infertility was 4.92 years with a range of 2 to 7 years. All the patients included in this study were earlier treated with 150 mg of clomiphene citrate for 5 to 14 cycles with a mean of around 8 cycles (Table 1). Significant differences involving the follicular size and endometrial thickness were found between CC and letrozole treated cycles. Mean follicular diameter was 11.86 $\pm$ 1.22 mm and 19.3 $\pm$ 1.94 mm in the CC and letrozole group respectively with a significant difference of P value of 0.05 (Table 2, Fig. 1).

Table 1: Characteristics of study population

Characteristics	*Mean ± SD*	*Range*
Age (Years)	31.31 ± 3.86	24-40
BMI (kg/m^2)	27.50 ± 2.92	23-32
Duration of infertilty (Years)	4.92 ± 1.77	2-7
No. of previous CC cycles	7.95 ± 3.22	5-14
Hormone level on day 2		
• FSH (mIU/ml)	5.33 ± 1.66	3.68-9.11
• LH (mIU/ml)	7.26 ± 2.29	3.35-13.29

BMI: Basal metabolic index, CC: Clomiphene citrate, FSH: Follicle stimulating hormone, LH: Luetinizing hormone.

Table 2: Response to CC *vs* letrozole in the study population

Parameters	*CC Mean ± SD*	*Letrozole Mean ± SD*	*P value*
Follicular size by D13/14 (mm)	11.86 ± 1.22	19.3 ± 1.94	< 0.05
Endometrial thickness (mm)	5.9 ± 0.84	9.4 ± 1.33	< 0.05

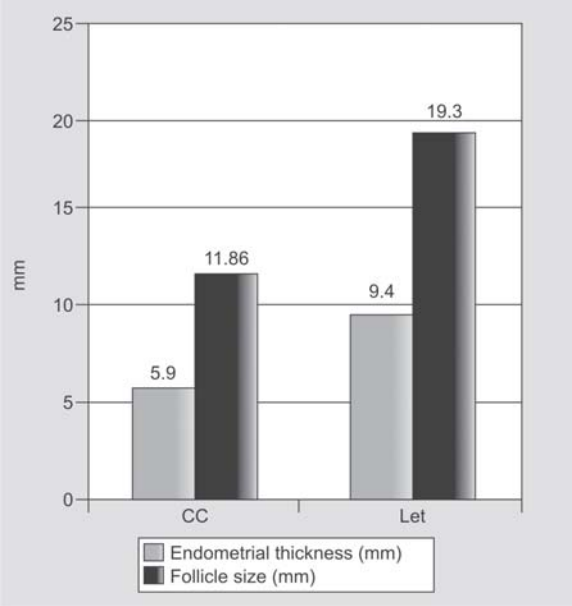

Fig. 1: Mean ET and mean FS in the CC and Let. Group. ET: Endometrial thickness, FS: Follicle size, CC: Clomiphene citrate, Let.: Letrozole

Table 3: Occurrence of ovulation (n = 60)

Parameter	*CC*		*Letrozole*
Ovulation	None(0%)	38 patients (63.33%)	12 patients responded to 5 mg dose 26 patients responded to 7.5 mg dose

Table 4: Pattern of mature follicular development in letrozole treated cycles

Parameter	*Multiple*	*Single (Mono)*
Type of follicle	26 patients (68.42%)	12 patients (31.58%)

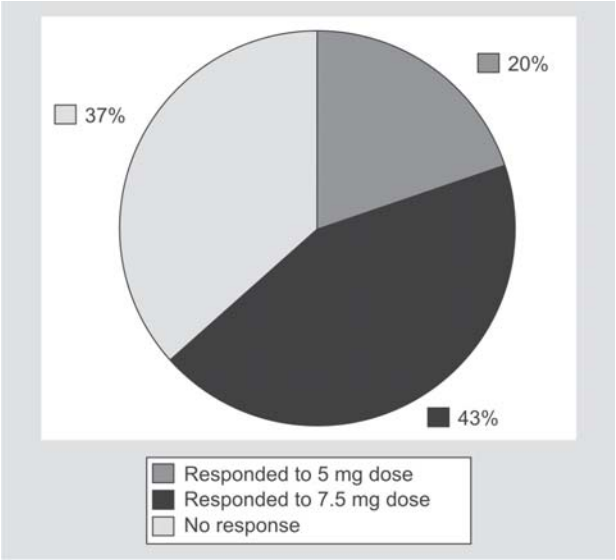

Fig. 2: Response of study population to letrozole

Mean endometrial thickness was 5.9 ± 0.84 mm in the CC treated cycle and 9.4 ± 1.33 mm in the letrozole group again with a P value of 0.05 which was found significant (Table 2, Fig. 1). Obviously none of the patients ovulated while being treated with CC, whereas ovulation occurred in 38 patients (63.33%) in the letrozole treated cycles (Table 3). 12 patients (31.58%) developed mature follicle at 5 mg dose of letrozole but the dose had to be increased to 7.5 mg in the remaining 26 patients (68.42%) (Fig. 2). Most of developed follicles (68.42%-26 pts) were multiple and single follicle developed in 12 patients (31.58%) (Table 4).

DISCUSSION

Ovulation is an important prerequisite for a successful pregnancy. Anovulation accounts for 20% of cases of infertility provided other factors are normal and PCOS is a main cause for anovulation. For years clomiphene citrate has been the drug of choice for induction of ovulation in PCOS patients. CC augments ovulation by blocking negative feedback of endogenous estrogen at the level of hypothalamus and pituitary, leading to an increase in the pulsatile release of FSH and LH. Unfortunately, CC is associated with a high induction rate but with a low pregnancy rate probably due to the antiestrogenic mechanism of CC, which involves long lasting estrogen receptor depletion leading to a thickened cervical mucous and thinning of endometrium. However, 20 to 25% patients do not respond to CC and a dose exceeding 150 mg is not yet recommended. In CC failures, next treatment option includes expensive and risky gonadotrophins difficult to afford for many of the patients in Bangladesh.

Letrozole belongs to a new group of very potent, non-steroidal, selective reversible third generation aromatase inhibitor developed for postmenopausal breast cancer therapy.[6] Letrozole inhibits the conversion of adrenally generated androstenedione to estrone or estradiol by aromatase enzyme in peripheral tissues.[12] It acts by competitive binding to the hem of cytochrome P450 subunit of the aromatase enzyme and interrupts the metabolism of estrogen resulting in a decrease level of estrogen in the body. As a negative feedback mechanism, the pituitary gland produces follicle stimulating hormone (FSH) leading to ovulation or superovulation. Therefore, letrozole generally mimics the action of CC without depletion of estrogen receptors when administered early in the menstrual cycle.[6] Because of the much shorter life span (2 days) and absence of estrogen receptor binding, it possibly avoids the antiestrogenic effects associated with CC.[6]

Over the recent years, letrozole has been studied at the University of Toronto as a fertility drug with satisfying results.[7] Their studies found that the drug appears to be completely eliminated from the body within a few days of the last tablet. So far there is no evidence that this drug has any harmful effects on the developing fetus. It therefore appears to be safe as a fertility drug. Letrozole is approved by the United States Food and Drug Administration (FDA) for the treatment of local or metastatic breast cancer that is hormone receptor positive in postmenopausal women. Infertility specialists have been using this drug for ovulation induction since 2001. However, like many other drugs (e.g. misoprostol), induction of ovulation by letrozole is an 'off-label' indication because it is not marketed for use as a fertility drug.[7]

In the present study, intervention in the form of 5 to 7.5 mg of letrozole was given to PCOS patients who did not respond well to CC earlier. All patients received 5 mg letrozole in the first cycle. Only those patients received a higher 7.5 mg dose who failed to respond to the initial dose. It was observed that majority of the patients responded well to the higher dose.

Because of the recent acceptance of letrozole as a fertility drug, only a few studies were available assessing the usefulness of letrozole in CC resistant patients.[21,23-25] Most of them are pilot studies or preliminary comparisons. Mitwally and Casper from University of Toronto reported a 75% success rate using 2.5 mg dose in a study of 12 anovulatory PCOS patients with an inadequate response to CC.[20] Begum MR et al[12] in her study at a tertiary referral infertility clinic at Dhaka, Bangladesh involving 35 anovulatory infertile patients nonresponsive to CC showed

a high success rate (77.77%) for follicular development using letrozole at 2.5 to 5 mg dose. Another survey by Badawy A et al[11] also reported a successful induction (62%) in PCOS patients using 5 mg letrozole previously treated with Clomiphene citrate. Our success rate of 63.33% cases using 5 to 7.5 mg of letrozole is comparable with these studies. Mean follicular size was 19.3 ± 1.94 mm using letrozole compared to 11.86 ± 1.22 mm when CC was used in the previous cycles. So, obviously the follicular size became significantly larger ($P < 0.05$) in the letrozole group. Endometrial thickness also increased from 5.9 ± 0.84 mm with CC to 9.4 ± 1.33 mm with letrozole also showing a statistical significance ($P < 0.05$). A recent study by Quintero RB et al[10] compared pregnancy rates (PR) for letrozole and gonadotrophins in a group of patients resistant to CC. They concluded that gonadotrophins had higher PR than letrozole, but the PR with letrozole was high enough to justify its use in this group of patients. Badawy et al[11] in his recent study compared the effects of 5 mg letrozole with 100 mg CC for ovulation induction in PCOS patients and suggested that ovulation rates were more or less similar in two groups without a statistically significant difference. Majority of the patients in this study, however, responded to a higher 7.5 mg dose in comparison to a relatively lower 2.5 to 5 mg dose in other studies.[5,8,9,11] That is probably because the study population in those studies also included anovulatory patients other than PCOS. In this study, majority of patients (68.42%) developed multiple follicles, which however contradicted the report of Begum MR et al[12] showing the development of a single follicle in 77.77% patients.

CONCLUSION

Clinical utilization of ovarian stimulation to facilitate the ability of a couple to conceive has not only provided a valuable therapeutic approach, but has also yielded extensive information on the physiology of ovarian follicular recruitment, endometrial receptivity and early embryocompetency. Anovulatory PCOS patients can be successfully treated by ovulation induction. In patients that failed to respond to the first line choice of CC, gonadotrophin injections and laparoscopic ovarian drilling are the next treatment options. In a less developed country like Bangladesh, monitoring expenses are high and laparoscopy facilities are limited. As a result, many of the patients find it difficult to afford these options and a few of them eventually become lost possibly due to lack of financial support. So, if a relatively inexpensive oral agent like letrozole can be used for this purpose even with a reasonable success rate, it would be an excellent alternative for this group of patients of developing world.

REFERENCES

1. Balen AH, Michelmore K. What is polycystic ovary syndrome? Are national views important? Hum Reprod 2002;17:2219-27.
2. Mitwally MF, Casper RF. Aromatase inhibitors in ovulation induction. Semin Reprod Med 2004;22(1):61-78.
3. Casper RF. Aromatase inhibitors: New experiments or new value. Updates in Infertility treatment 2004 Seminar in Florida 22-24 .
4. Wessman A, McArdle CR, Achiron R. Ultrasound in Infertilty. Infertility: A comprehensive text (2nd ed). Appleton and lange 1996;0447-92.
5. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75(2):305-09.
6. Casper RF. Aromatase inhibitors: New experiments or new value? Updates in infertility treatment. Marco Island Florida January 2004;22-24 .
7. Hudson Stephen. Infosheet: Letrozole. Victoria Fertility Center.#207-4400 Chatterton Way Victoria BC V8X 5J2. www.victoriafertility.com.
8. Begum MR, Quadir E, Begum A, Begum RA, Begum M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. J Obstet Gynaecol Res Oct 2006;32(5):502-06.
9. Badawy A, Mosbah A, Shady M. Anastrozole or letrozole for ovulation induction in clomiphene resistant women with polycystic ovary syndrome: A prospective randomized trial. Fertil Steril Aug 2007;7.
10. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotrophins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertil steril Oct 2007;88(4):879-85.
11. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozol for ovulation induction in women with polycystic ovary syndrome: A prospective randomized trial. Fertil Steril Jun 2007;18.
12. Begum MR, Siddiqui M. Aromatase Inhibitors: Types, Mode of action and Indications: Jean R Lamonte (Eds). Nova Science Publishers: USA 2009.
13. Hommburg R, Insler V. Ovulation Induction in perspective. Hum Reprod Update 2002;8:449-62.
14. Bayar U, Basaran M, Kiran S, Coskun A, Gezwe S: Use of an aromatase inhibitor in patients with polycystic ovary syndrome: A prospective randomized trial. Fertil Steril Nov 2006;86(5): 1447-51.
15. Fatemi HM, Kolibianakis E, tournaye H, Camus m, Steirtegham Van AC, et al. Clomiphene citrate versus letrozole for ovarian stimulation: A pilot study. Reprod Biomed Online Nov 2003;7(5):543-46.
16. Casper RF, Mitwally MF. Review: Aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab Mar 2006;91(3):760-71.
17. Homburg R. Oral agents for ovulation induction-clomiphene citrate vs aromatase inhibitors. Hum Fertil (Camb) Mar 2008;11(1):17-22.
18. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006;85(2):277-84.
19. Franks S. Polycystic ovary syndrome. N Engl J Med 1995; 333:853-86.
20. Mitwally MF, Casper RF. Potential of aromatase inhibitors for ovulation and superovulation induction in infertile women. Drugs 2006;66(17):2149-60.

21. Bayar U, Tanriverdi HA, Barut A, Ayoglu F, Ozcan O, et al. Letrozole vs clomiphene citrate in patients with ovulatory infertility. Fertil Steril Apr 2006;85(4):1045-48.
22. The ESHRE Capri workshop. Female infertility: Treatment options for complicated cases. Hum Reprod 1997;12:1191-96.
23. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertil Steril Dec 2004;82(6):1561-63.
24. Noriega-Portella L, Noriega-Hoces L, Delgado A, Rubio J, Gonzales GF. Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril Dec 2007;14.
25. Topipat C, Choktanasiri W, Jultanmas R, Weerakiet S, Wongkularb A, et al. A comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on superovulation in Asian women with normal ovulatory cycles. Gynecol Endocrinol Mar 2008;24(3):145-50.