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Research

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Optimized Letrozole Dose *Versus* Traditional Use of Clomiphene Citrate for Ovulation Induction in Patients With PCOS: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: To compare the effects of gradually increased letrozole dose in *versus* Clomiphene Citrate (CC) (100 mg) for ovulation induction in women with polycystic ovary syndrome (PCOS).
Design: Prospective randomized controlled trial.
Setting: IVF unit at Minia Maternity University Hospital in Egypt.
Patient(s): Two hundred infertile women with PCOS defined according to Revised Rotterdam criteria.
Intervention(s): patients were randomly allocated into two groups; study group (100 patients) receiving gradually increased doses of letrozole starting with 2.5 mg on cycle day 3 with incremental increase of 2.5 mg daily till reaching a dose of 10 mg daily on cycle day 6 and a control group (100 patients) receiving CC at a dose of 100 mg daily for 5 days starting from cycle day 3. Patients were followed up for three treatment cycles. The primary outcome was clinical pregnancy rate and the secondary outcome was number of mature follicles, endometrial thickness, serum progesterone and time to reach a dominant follicle.
Result(s): The two groups were similar in the demographic features and baseline hormonal milieu. There was no significant difference between the two groups as regards the number of mature follicles and the time to reach mature follicles. Endometrial thickness on HCG day was significantly higher in the letrozole group as compared with CC group (10.1±0.22 mm *vs* 8.2±0.69 mm, p=0.01)). Serum progesterone was higher in letrozole group than in CC group (19.3±3.1 *vs* 15.3±2.2, p<0.01). Ovulation was achieved in165/242 cycles (68.2 %) in the letrozole group and 169/249 cycles (67.9 %) in the CC group which was not statistically significant. Clinical pregnancy rate was significantly higher in letrozole group in comparison with CC group (14.8 % *vs* 10.4 %, p<0.01)
Conclusion(s): Letrozole in gradually increased dose achieves higher clinical pregnancy rate as compared with the traditional dose of CC. Therefore, it can be used as a first-line treatment for ovulation induction in women with PCOS.

KEYWORDS: Polycystic ovary syndrome; Letrozole; Clomiphene citrate; Ovulation induction.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory disorder in young women. It can be manifested in a variety of clinical presentations. It is estimated that 55% to 75% of women with PCOS are infertile due to chronic anovulation.[1,2] Clomiphene Citrate (CC) is still the first line treatment for ovulation induction. However, there is a marked discrepancy between ovulation rate and pregnancy rate achieved with CC which can be attributed to the negative effect on the cervical mucus and endometrium.[3,4]

Letrozole is a type II a third-generation aromatase inhibitor that has been widely used in women with breast cancer.[5] It works through inhibiting the conversion of and rostenedione

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and testosterone to estrogen in the ovary which leads to estrogen depletion that creates negative feedback signals to hypothalamic-pituitary axis (HPA), therefore, follicle-stimulating hormone (FSH) secretion increases, stimulating the development of ovarian follicles.[6-9]

The aim of the current study was to compare the effects of gradually increased dose of letrozole *versus* the traditional dose of CC for ovulation induction in in infertile women with PCOS.

PATIENTS AND METHODS

This study is a randomized controlled trial including 200 women with PCOS recruited from those attending the Fertility unit at Minia Maternity University Hospitalin Egyptin the period from January 2013 to January 2014. Ethical approval for the study was obtained from the local ethical committee of the department of Obstetrics and Gynecology. All the eligible women signed a written informed consent before inclusion in the study. .

Inclusion criteria of the study were: a) Age from 18 to 35 years b) diagnosis of PCOS according to revised Rotterdam criteria,[10] c) Patent fallopian tubes proved by hysterosalpingography (HSG), d) normal semen analysis of the male partner according to the modified criteria of the World Health Organization.[11] We excluded patients with: a) history of laparoscopic ovarian drilling, b) uterine cavity abnormalities, and c) combined factors of infertility.

RANDOMIZATION

Patients were randomly allocated using a computer-generated random table into two groups:

• Study (letrozole) group (n=100):in this group, patients received letrozole (Novartis Pharma Services, Basel, Switzerland) starting with a dose 2.5 mg on cycle day 3 with 2.5 mg incremental increase in the dose till reaching a dose of 10 mg on cycle day 6.

Control (CC) group (n=100): in this group, patients received CC (Hoechst Marion Roussel, ARE) at a dose of 100 mg daily for 5 days starting from cycle day 3. The study flow chart is shown in Figure 1.

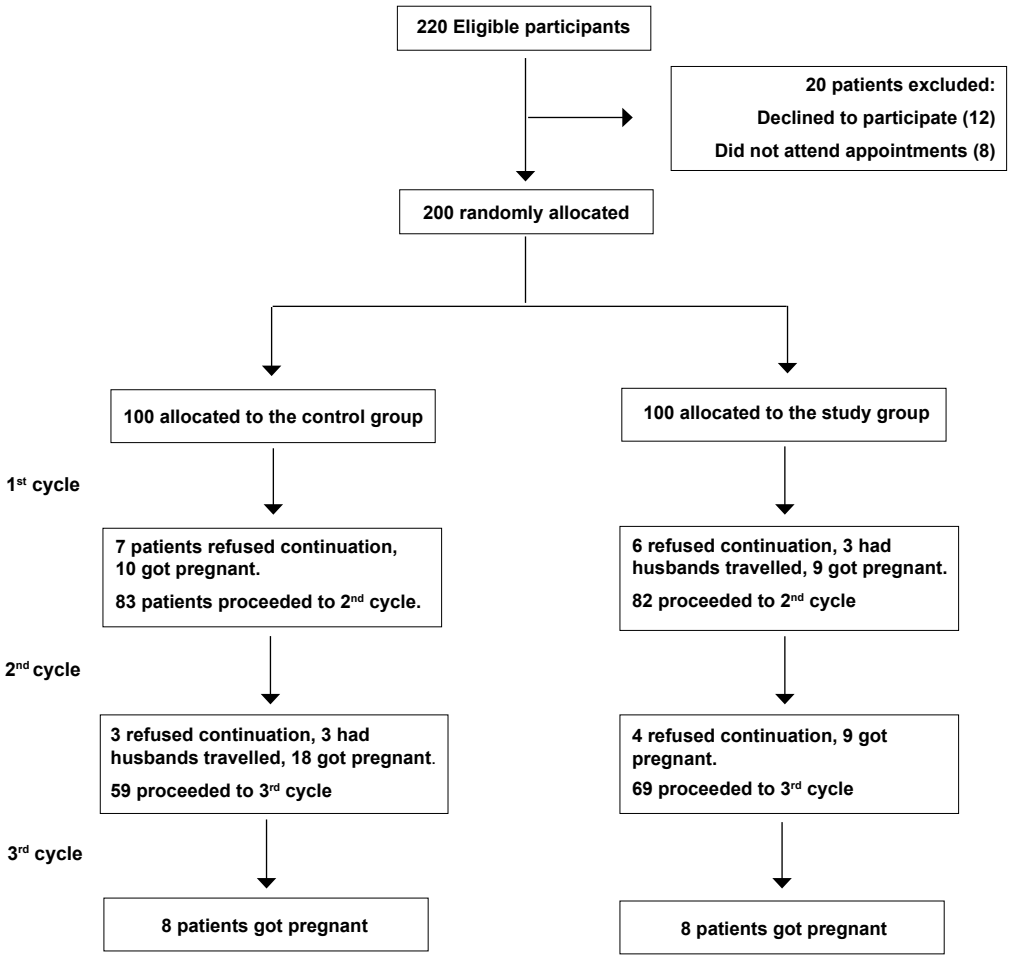

Figure 1: Study flow chart.

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Patients were monitored with transvaginal ultrasound starting from the 6th day of stimulation and every other day till a dominant follicle reaching 18 mm in diameter. Human chorionic gonadotropin (hCG) injection (5000-10,000 IU IM) was commenced when at least one follicle measuring 18 mm was detected on ultrasound scan. Serum progesterone (ng/mL) concentration was measured on days 21 to 23 of the cycle by radioimmunoassay (RIA) using the antibody coated tube method (Coat-A-Count; Diagnostic Product Corporation, Los Angeles, CA). Patients were advised to have intercourse 24 to 36 hours after the hCG injection. Serum pregnancy test was performed two weeks after the hCG injection. Clinical pregnancy was confirmed by detection of fetal pole and pulsation with ultrasound scan two weeks after a positive pregnancy test. If no pregnancy was achieved in the first cycle, the same treatment was given for a total of three treatment cycles.

OUTCOME MEASURES

• The primary outcome measure of the study was the clinical pregnancy rate.

• The secondary outcome measures were the number of mature follicles, endometrial thickness, serum progesterone and the time to reach a dominant follicle.

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package for Social Science (SPSS) version 17. Data were presented as mean and standard deviation (SD) for continuous variables, frequencies and percentages for categorical data. Chi square test was used to compare categorical data A $p<0.05$ % was considered statistically significant.

RESULTS

The study included 200 patients received 491 treatment cycles. There were no statistically significant differences between the two groups as regards the demographic features and hormonal milieu as shown in Table 1.

There was no significant difference between the two groups as regards the number of mature follicles and the time to reach mature follicles. Endometrial thickness on HCG day was significantly higher in the letrozole group as compared with CC group (10.1±0.22 mm *vs* 8.2±0.69 mm, $p=0.01$)). Serum progesterone was higher in letrozole group than in CC group (19.3±3.1 *vs* 15.3±2.2, $p<0.01$). Ovulation was achieved in 165/242 cycles (68.2 %) in the letrozole group and 169/249 cycles (67.9 %) in the CC group which was not statistically significant. Clinical pregnancy rate was significantly higher in letrozole group in comparison with CC group (14.8 % *vs* 10.4 %, $p<0.01$). There was one case of twin pregnancy in the CC group, but no ovarian hyperstimulation syndrome (OHSS) occurred in either group. (Table 2)

DISCUSSION

CC is most commonly used drug for ovulation induction in patients with PCOS. However, it has anti-estrogenic effect so it may be associated with poor cervical mucus and endometrial thinning due to prolonged estrogen-receptor depletion in the endometrium and possibly in the cervix; an effect that can explain the obvious discrepancy between the ovulation rate and the pregnancy rate achieved with CC.[3,4]

Letrozole; an aromatase inhibitor, has been tried by many researchers as an alternative treatment to CC in different

	Letrozole group (n=100)	CC group (n= 100)	*p* value
Age	24.8±3.1	25.3±2.9	0.67
Type of infertility:			
-Primary	67 (67 %)	71 (71 %)	0.74
-Secondary	33 (33 %)	29 (29 %)	
Duration of infertility(years)	4.1±3.1	5.1±2.2	0.81
BMI(kg/m2)	31.1±2.91	29.1±3.12	0.31
Clinical presentation			
Oligo/anovulation	95 (95 %)	92 (92 %)	0.75
Hyperandrogenism	44 (44 %)	42 (42 %)	0.68
Polycystic ovaries	85 (85 %)	70 (70 %)	0.08
FSH (IU/l)	6.1±2.92	6.3±2.2	0.63
LH (IU/L)	12.9±1.82	12.1±3.11	0.52
Testosterone(ng/ml)	0.62±0.3	0.61±0.2	0.64

Data is presented as mean±SD or number and percentage.

Table 1. Demographic features and hormonal profile of the study population.

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-3-128

	Letrozole group (n=100)	CC group (n=100)	*P* value
No. of stimulation cycle	242	249	0.83
No. of follicles (≥18 mm) on the day of hCG	3.4±0.5	3.8±0.6	0.04*
Endometrial thickness on the day of hCG	10.1±0.22	8.2±0.69	0.01*
Serum progesterone on day 21-23(ng/ml)	19.3±3.1	15.3 ± 2	<0.01*
Timeto reach a dominant follicle (days)	10.1±1.32	10.3±1.8	0.21
Clinical pregnancy rate per treatment cycle	36/242 (14.8 %)	26/249(10.4 %)	<0.01*
Multiple pregnancy	0	1	0.5
OHSS	0	0	0.93

Data is presented as mean±SD
*Statistically significant.

Table 2: Details of stimulation cycles and outcome measures in the study population.

regimens.[12-18] The optimal dose of letrozole for ovulation induction in patients with PCOS has not been yet determined. Most of the published studies had used letrozole in a fixed dose (2.5-7.5 mg) starting from cycle day 2 to 6. A novel step-up protocol of letrozole was used by Mitwally et al.[19] This study included 22 PCOS women in whom 9 women received letrozole in a step-up protocol consisting of one, two, three, and four tablets of letrozole (2.5 mg) daily on menstrual cycle days 2, 3, 4, and 5, respectively. The control group included 13 patients received 100 mg/day clomiphene citrate (CC) for 5 days starting on menstrual cycle day 3. The step-up letrozole protocol in that study was shown to achieve higher CPR per treatment cycle as compared with CC. The CPR per cycle reported by Mitwally et al was 27.3 % which is higher than the rate reported in the current study (14.8 %). The cause for this marked difference may be attributed to the use of intrauterine insemination in the first study while in the current study; patients were advised to have timed intercourse in addition to the relatively small number included in the first study.

Elham Rahmani et al used a step up protocol with serial increase in letrozole dose over three successive months of treatment. They started with 2.5 mg and the dose was increased according to response. They concluded that increasing the dose can improve the chance of ovulation and pregnancy.[20] However, we believe the protocol used in that study is consuming time and raises the cost of the treatment.

Mitwally and Casper[21] gave letrozoleat a fixed dose of 2.5 mg starting from cycle day 3 for 5 days in 12 patients with PCOS. Ovulation occurred in nine patients (75 %), and pregnancy was achieved inthree patients (25 %). In the current study letrozole was given with gradual increase of the dose started with 2.5 mg to reach 10mg to maximize the effect of letrozole in ovulation induction and try to decrease side effects (OHSS and multiple pregnancies) and at the same time reduce the cost of treatment per cycle. Clomiphene citrate results in central estrogen receptor depletion for a long duration because of its significantly greater half-time for clearance (2 weeks).[22,23] As a result, supra-physiological levels of estrogen can occur without central suppression of FSH because the normal estrogen receptor-mediated feedback mechanisms are blocked. This results in multiple follicle growth and in higher multiple pregnancy rates with CC than encountered with aromatase inhibitor cycles. Mitwally et al.[24] reported favorable pregnancy outcomes and a low multiple-gestation rate for the use of aromatase inhibitors for ovarian stimulation.

In the present study, CPR was higher in the letrozle group despite there was no significant difference in the number of mature follicles between the two groups. This can be explained by the adverse effect of CC on the endometrium and cervical mucus. This finding is not in agreement with Al-Fouzan et al who reported higher number of mature follicles in the letrozole group than in the CC group.[17] Endometrial thickness was significantly higher in letrozole group in the current study. Similar findings were reported by Mitwally and Casper.[21] Cortinez et al also reported normal morphologic features of endometrium and full expression of pinopodes during the implantation window when letrozole was used,[15] while Kilic et al and Bishai et al noted significant effect of both drug on the endometrium.[25,26]

Data about teratogenic capacity of letrozole in humans is lacking. Animal studies have shown that low doses of letrozole are effective in inducing noxious effects on the developing conceptus.[26] Large randomized controlled trials are required to evaluate the long term safety of letrozole use for induction and its optimal dose to balance between better pregnancy and neonatal outcome.

In conclusion, Letrozole in gradually increased dose is associated with higher CPR as compared with the traditional CC dose for ovulation induction in women with PCOS. Further studies are needed to confirm these findings and to provide stronger evidence for implication of such regimen in clinical practice.

CONFLICTS OF INTEREST: None.

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