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To Study the Efficacy on Fertility Outcome by short term Letrozole versus Extended Letrozole Regimen in Clomiphene Citrate Resistant PCOS Women

Authors
Dr Poonam Yadav[1], Dr Mohita Agarwal[2], Dr Vishy Agarwal[3], Dr Urvashi Verma[4] Dr Rachana Agarwal[5]
[1,2,4,5]Associate Professor, Department of Obstetrics & Gynaecology, Sarojini Naidu Medical College, Agra
[3]Senior Resident, Department of Obstetrics & Gynaecology, Sarojini Naidu Medical College, Agra

Abstract
Introduction: *Polycystic ovary syndrome (PCOS) is the most common condition associated with chronic anovulation affecting 4– 6% reproductive age group, letrozole has been used successfully for ovulation induction in patients with PCOD and unexplained infertility.*
Aim: *The aim was to study the efficacy on fertility outcome by short term letrozole versus extended letrozole regimen in clomiphene citrate resistant PCOS women.*
Material & Method: *It was a prospective study in which 105 women with clomiphene resistant PCOS were randomly allocated in two groups. Group 1 having 55 patients receives letrozole in a dose of 2.5 mg for 5 days while the group 2 having 50 patients receives letrozole in a dose of 2.5 mg for 10 days.*
Result: *The ovulation rate, total number of follicles in the short term letrozole was 60.4% and 3.5±0.5 in the short term letrozole group while it was 67.3% and 6.8 ± 0.3 in the long letrozole group respectively. In our study the the endometrial thickness and serum estradiol level on day 10 was 10.2±0.2 and 240±46 in the short letrozole group while it was 11.4±0.6 and 338±70.4 in the long letrozole group respectively .The results of our study shows that the in the short letrozole group the pregnancy rate was 12.5% and miscarriage rate was 16.7% while it was 18.3% and 11.1% in the long letrozole group respectively.*
Conclusion: *The results of this study suggests that by extending the duration of letrozole therapy in midfollicular phase the FSH levels were maintained above the threshold allowing multifollicles to develop and leads to better ovulation and pregnancy rate.*
Keywords: *PCOS, Clomiphene citrate resistant PCOS, letrozole, extended letrozole therapy.*

Introduction

The polycystic ovary syndrome (PCOS) is the most common condition associated with chronic anovulation affecting 4– 6% reproductive age group. Several mechanism contribute to the pathophysiology of PCOS, operating at every level of the reproductive system. It is inaccurate to state that PCOS is the most common cause of anovulation, because PCOS is the consequence of chronic anovulation, which can result from a wide variety of the causes.

Dysovulaory causes accounts for approximately 30 -40% of all cases of female infertility but are generally easily diagnosed and are the most treatable cause of infertility. The drug of first choice for ovulation induction is clomiphene citrate (CC). It has been the first line therapy for induction of ovulation in women with anovulatory infertility. It is nonsteroidal triphenylethylene derivative with estrogen agonist and antagonist properties. However, about 20% of women failed to ovulate inspite of increasing dose of this drug, upto 150 mg.

It induces prolonged estrogen receptors depletion and thus exerts antiestrogenic effect on endocervix and endometrium and also associated with the risk of ovarian hyperstimulation syndrome[1]. Several studies revealed that its adverse effect on cervical mucus quantity and quality leads to implantation failure.

CC – resistance refers to the failure to ovulate with 150 mg of CC for atleast 3 cycles, while CC – failure[2] is defined as failure to conceive with CC despite successful regular ovulation for 6 – 9 cycles.

Alternative methods used for the ovulation induction in clomiphene citrate PCOS women are the CC in combition with metformin, CC in combition with dexamethasone, selective aromatse inhibitor such as letrozole and anastrozole, gonadotropins, laproscopic ovarian diathermy.

Nowadays, letrozole has been used successfully for ovulation induction in patients with PCOD and unexplained infertility[3] .In contrast to clomiphene citrate letrozole is rapidly eliminated from the body and does not deplete estrogen receptors and therefore has no adverse effect on endometrium or endocervix.[4,5]

Letrozole is a third generation, potent, reversible, non steroidal aromatase inhibitor. Its administration in early follicular phase blocks estrogen synthesis by inhibiting aromatase as a result of which FSH and LH level increases due to negative feedback causing recruitment and growth of antral follicles[6]. But it has short half life (average 45 hours) due to which effect decreases in late follicular phase causing decrease in the level of FSH and this drop causes atresia of all follicles other than dominant follicle leading to mono –ovulation. However, the advantage of extended letrozole regimen is that it maintains the decrease estrogen level for a longer period consequently increased FSH level is maintained even in the late follicular phase leading to the development of multiple follicles.[7]

In different studies letrozole used in various doses for clomiphene citrate-resistant infertile women with PCOS are 2.5, 5 and 7.5 mg per day in each cycle.

Aims and Objectives

To study the results of short term versus extended letrozole regimen in clomiphene citrate resistant PCOS women in terms of ovulation and pregnancy

Material and Methods

This is a prospective comparative study comprising 105 women with clomiphene resistant PCOS attending the gynaecology O.P.D., in Department of Obstetrics and Gynaecology, S.N. Medical College Agra from the period of April 17 to March 18

Inclusion Criteria

Patients having age 20 -35 years with primary or secondary infertility having clomiphene resistant PCOS, patent fallopian tubes proved by hysterosalpingography, normal husband semen analysis with normal serum prolactin, thyroid stimulating hormone and serum estradiol.

Exclusion Criteria

Patients having age less than 20 yrs or more than 35 yrs, patients with tubal obstruction, patients with endometriosis, FSH >10 mIU /L, patients with liver or kidney disease and with male factor subfertility

These patients were randomly allocated into 2 groups

Group 1: 55 patients received letrozole in a dose 2.5mg/day from cycle day1 – day5.

Group 2: 50 patients received letrozole in a dose 2.5mg/day from cycle day1 - day 10
Withdrawal bleeding was achieved in an amenorrhoeic patients by giving the progesterone. Patients who had S.LH >7 prescribed with 2 cycles of oral contraceptive pills (ethinyl estradiol and cyproterone acetate) Day 2 ultrasound including the baseline scan and endometrial thickness , Day 2/3 gonadotropins levels were done in all the patients of both the group.

Short Letrozole Regimen

Letrozole was given to 55 patients in dose of 2.5 mg starting from day 1 of the menses for 5 days . Starting from the cycle day 8 , ultrasound scans were repeated every 2 -3 day to monitor follicle growth .Serum estradiol was measured on D_{10} . Endometrial thickness were measured at the greatest diameter perpendicular to the midsagittal plane in the fundal region. The numberof dropouts in this group were 3 patients. Total number of cycles taken into consideration were 96

Extended Letrozole Regimen

Letrozole was given to 50 patients in dose of 2.5 mg starting from day 1 of the menses for 10 days. Starting from the cycle day 8 ultrasound scans were repeated every 2-3 day to monitor follicle growth. Serum estradiol and endometrial thickness were measured. The number of dropouts in this group were 2 patients. Total number of cycles taken into consideration were 98.
Human chorionic gonadotropin was administered to trigger ovulation when at least one follicle measuring more than 18 mm in mean diameter was found in transvaginal ultrasonography and patients were advised for intercourse after 24 – 36 h of human chorionic gonadotropin of injection. They were then called after 17 -18 days for urine pregnancy test.
Primary endpoints was no. of follicle >18mm, ovulation and endometrial thickness at the time of hCG administration. Secondary endpoints was ongoing pregnancy defined as viable pregnancy of atleast 12 weeks, miscarriages and multiple pregnancy.

Statistical analysis and study resign

The sample size was calculated using the appropriate formula Z2PQ/d2 where P and Q taken as 0.5 to get the maximum sample size with 10 % non response rate with 85 percent confidence interval . The data were entered in MS Exel and analysed using SPSS ver 18.Results were expressed as mean and standard error of the mean. The difference were considered to be stastically significant with $p < 0.05$at 95% CI.

Results

Table 1 Distribution of patients according to age , BMI and type of infertility

AGE (yrs)	Short Letrozole Gp.(n=52)	Extended Letrozole Gp.(n=48)
21 – 25	15	12
26 – 30	28	29
31 – 35	09	07
BMI		
Underweight <19	02	02
Normal 19.1 – 24.9	19	16
Overweight 25 -29.9	26	27
Obese >30	05	03
TYPE OF INFERTILITY		
Primary	45	42
Secondary	07	06

Table 2 Distribution of patients according to Day 2/3 Gonadotropins levels

	Short Letrozole Gp(n=52)	Extended Letrozole Gp.(n=48)	P value
Serum FSH (IU/L)			
4 -6	48	42	
6 -8	03	04	
8-10	01	02	
Mean	5.30 ±0.79	5.10± 0.68	0.274
Serum LH (IU/L)			
5-10	28	26	
10-15	22	21	
15-20	02	01	
Mean	8.60 ±1.2	8.87± 1.5	0.34

Table 3 Distribution of cycles according to rate of ovulation, total number of follicles and follicular size

	Short Letrozole Gp (n=96 cycles)	Extended Letrozole Gp.(n=98cycles)	P value
No. of ovulatory cycles	58(60.4%)	66(67.3%)	
Total number of follicles during stimulation	3.5± 0.5	6.8± 0.3	0.01
No. of follicles >14 mm	2.2±0.5	3.8±0.4	0.03
No. of follicles >18mm	1.6±0.4	3.2±0.3	0.03

Table 4 Disribution of patients according to endometrium thickness ET (mm) and Serum estradiol D_{10} (pg/ml)

	Short Letrozole Group		Extended letrozole Group		P value
Endometrial thickness (mm)	Pre treatment	Post treatment	Pre treatment	Post Treatment	
	4.4±0.5	10.2±0.2	4.6±0.3	11.4±0.6	0.88
S.estradiol D_{10} (pg /ml)	240 ±46		338±70.4		0.07

Table 5 Distribution of cycles according to pregnancy rate, miscarriage rate and multiple pregnancy.

	Short Letrozole Gp(n=96cycles)	Extended letrozole Gp.(n=98cycles)
Pregnancy rate	12(12.5%)	18(18.3%)
Miscarriage rate	**2 (16.7%)**	**2 (11.1%)**
Multiple pregnancy	0	2

A total 105 patients were eligible to participate in the study after evaluating the exclusion criteria. Out of which 3 patients from the short letrozole group and 2 patients from the extended letrozole group did not completed the study protocol. So the results of the remaining 100 patients (194 cycles) in total were analysed There was no statistical significant difference between the two groups regarding the age, body weight, height and body mass index (BMI).(Table 1)

Mean of basal serum FSH was 5.30 ±0.79 in the short letrozole group and 5.10±0.68 in the extended letrozole group. The difference between the two was not statistically significant (p >0.05). The mean of basal serum LH was 8.60 ±1.2 in the short letrozole group and 8.87±1.5 in the extended letrozole group. The difference between the two was also not statistically significant (p >0.05). (Table 2)

Number of the ovulating patients in the short letrozole group was 60.4% and in the extended letrozole group was 67.3%. Total number of follicles during stimulation significantly greater in the extended letrozole regimen (6.8 ±0.3) than in the short letrozole regimen (3.5±0.5) and the difference between the two was statistically

significantly (p=0.01) The total number of follicles ≥14mm and ≥ 18 mm in the short letrozole group was 2.2±0.5 and 1.6±0.4 respectively while in the extended letrozole group it was 3.8±0.4 and 3.2±0.3 respectively . The total number of follicles of size >14 mm and >18 mm is greater in the extended letrozole group than the the short letrozole group and the difference between the two was statistically significant (p<0.05). (Table3)

In the short letrozole group the mean endometrial thickness increases from 4.4±0.5 to 10.2 ±0.2 and the mean serum estradiol level increases from the 102±40.8 to 310 ±4.60 while in the extended letrozole group the mean endometrial thickness increases from 4.6±0.3 to 11.4 ±0.6 and the mean serum estradiol level increases from the 100.6±38 to 338 ± 70.4.It was found that the difference in the postreatment endometrial thickness and in the postreatment serum estradiol levels between the two groups was not statistically significant (p >0.05) (Table 4)

In the short letrozole group the pregnancy rate was 12.5%, miscarriage rate was 16.7% and none of the patients had multiple pregnancy while in the extended letrozole group the pregnancy rate was 18.3% ,miscarriage rate was 11.1% and 2 patients had the multiple twin gestation.(Table5)

Discussion

In the present study the number of maturing follicles are more in the extended letrozole group than in the short letrozole group and this is in accordance to the study conducted by Badawy A et al in which 218 patients with the clomiphene citrate resistant PCOS were randomized to receive letrozole 2.5 mg from cycle day 1 to 10 or letrozole 5 mg/day from cycle day 1 to 5 and the result shows that the extended letrozole regimen resulted in more ovulatory cycles and also more number of mature follicles.[8]

In natural cycles the rise of FSH levels during the luteal – follicular transition phase stimulates the recruitment and growth of the cohort of antral follicles. The increased estradiol levels by the growing follicles suppresses FSH levels below the threshold and this leads to the selection of the dominant follicle which is sensitive to FSH as a result of which it continues to grow while the other suppressed.

Badawy et al suggested that the extended letrozole regimen can maintain FSH levels above the threshold required for the growth of follicles smaller than dominant follicle (i.e. widen FSH window) and therefore induces multiple ovulation.

In the present study the post-treat mentment endometrial thickness was 11.4 ±0.6 mm in the extended letrozole regimen which was greater than the short letrozole group in which it was 10.2±0.2 mm. Similarly the estradiol levels on D_{10} was 240 ±46pg / ml in the short letrozole group and 338±70.4pg/ml in the extended letrozole group. This is in accordance to the increase estradiol production due to the maturation of the greater number of the follicles. The results of our study are in agree with the results of the study by Al Fadhli et al[9] which shows that the ovulation rate and pregnancy rate was 1.9 and 18% respectively in a group which receives letrozole in a dose of 20 mg while it was lower i.e . 1.7 and 15% in a group which receives letrozole in a dose of 12.5mg.

On comparing in the short letrozole group the pregnancy rate was 12.5% and the miscarriage rate was 16.7 % while in the extended letrozole group it was 18.3% and 11.1% respectively and these results were consistent to the study by Badawy and Alaa Mosbah in which the pregnancy rate was 12.4% and the miscarriage rate was 18.4 % in the short letrozole group while it was 17.4% and 17.9% in the long letrozole group respectively.

In the present study there was 2 cases of multiple pregnancy in the extended letrozole group and none in the short letrozole group and this can also be explained on the basis that that the extended letrozole regimen can maintain FSH levels above the threshold (i.e. widen FSH window) and therefore induces multiple ovulation.

Conclusion

Thus it was suggested that the concept of extending FSH window by administering exogenous FSH or extending the duration of letrozole therapy in the midfollicular phase would maintain the FSH above the threshold allowing multifollicles to develop. This new 10 days letrozole protocol appears to be more effective than the standard 5 day protocol with more mature follicles and more pregnancy rate. However large randomized controlled trials are needed to establish standard letrozole regimen for ovulation induction.

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