Original Research

A Comparative Study Of The Efficacy Of Fertility Outcome By Short Term Letrozole Versus Extended Letrozole Regime In Infertile Patients With Anovulatory Cycles

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ABSTRACT

Background: Infertility is defined as failure to achieve pregnancy within 12 months of unprotected intercourse or therapeutic donar insemination in women younger than 35 years or within 6 months in women older than 35 years. In WHO classification of anovulation, Group 2 i.e. Hypothalamic-pituitary dysfunction is most common which is characterized by irregular or anovulatory menses, normal FSH, estrogen, and prolactin. Letrozole , is third generation, potent , reversible non steroidal aromatase inhibitor plays a pivotal role in the treatment of anovulatory infertility. Due to negative feedback FSH and LH level increases which leads to recruitment and growth of antral follicles. The short term regimn letrozole approach ovulation with minimal risk of adverse effect on endometrium thereby preserving endometrial receptivity and optimising condition for embryo implantation. use of extended regimn letrozole lies its ability to maintain low estrogen levels and sustain the inhibitory effect on aromatase enzyme activity throughout the follicular phase ,thereby promoting follicular growth and enhancing the likelihood of achieving a mature dominant follicle.

Objective: A Comparative Study of the efficacy of fertility outcome by short term letrozole versus extended letrozole regime in infertile patients with anovulatory cycles.

Method: This is a prospective comparative study comprising of 80 women with anovulatory cycles attending the gynaecology OPD in Department of Obstetrics and Gynaecology, of F.H.M.C. Etmadpur ,Agra from the period Jan 2023 to Dec 23. After full filling the inclusion criteria total number of participants divided in two group each having 40 participants. Group A – Extended protocol 2.5mg/day X 10days (D1-D10 of menses),.Group – Short protocol 5mg/day X 5days (D2-D7 of menses). Patients were followed from day 11 of the menses for follicular monitoring via USG till dominant follicle become 18 mm in size and a trigger of hcg 5000IU given i/m and rupture of follicle is monitored. Patient is followed after 14 days of trigger with UPT report. Outcome was measured in term of viable pregnancy.

Result: Thisstudy suggest that extended letozole therapy shows more no of growing follicles, more ovulation rate ,more no of pregnancy but data is not statistically significant.

Conclusion: It was accepted that by extending the letrozole therapy in midfollicular phase would maintain the FSH window prolonged allowing multifolliculardevelopement. this extended protocol appears to be more effective than the conventional short protocol with more no of matured follicles and more clinical pregnancy rate

Keywords: Infertility, Anovulatory cycle, Aromatase inhibitor , Letrozole

INTRODUCTION

Infertility is defined as failure to achieve pregnancy within 12 months of unprotected intercourse or therapeutic donar insemination in women younger than 35 years or within 6 months in women older than 35 years[1]. Primary infertility is the inability to have any pregnancy, while secondary infertility is the inability to have a pregnancy after previously successful conception[2].In WHO classification of anovulation, Group 2 i.e. Hypothalamic-pituitary dysfunction is most common which is characterized by irregular or anovulatory menses, normal FSH,

estrogen, and prolactin[3].

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

The Poly cystic ovary syndrome (PCOS) is the most common condition associated with chronic anovulation affecting 4-6% reproductive age group. It is the largest single cause of anovulatory infertility (80%)[5]. The underlying It is inaccurate to state that PCOS is the most common cause of anovulation , because it is the consequence of chronic anovulation.Dysovulatory causes accounts for approximately 30-40% of all cases of female infertility but are generally easily diagnosed and treatable. Letrozole , is third generation, potent , reversible non steroidal aromatase inhibitor plays a pivotal role in the treatment of anovulatory infertility. Inhibition of estrogen synthesis by AIs is dose dependent[6] They may be subdivided into steroidal (type I) and nonsteroidal (type II) inhibitors, which interact with the aromatase enzyme[7]. Due to negative feedback FSH and LH level increases which leads to recruitment and growth of antral follicles[8]. it does not posses anti estrogeniceffects on the endometrium therebyminimising the risk of thinning endometrial lining , which can impair implantation. Additionaly letrozole 's short half life allows for more precise control over ovarian response and reduced risk of ovarian hyper stimulation ,making it safer option for mono-ovulation. It has gained wide spread acceptance and utilisation in clinical practice due to its simplecity, efficacy, and favourable safety profile. The short term regimn letrozole approach ovulation with minimal risk of adverse effect on endometrium thereby preserving endometrial receptivity and optimising condition for embryo implantation .despiteit's efficacy and convinience this regimn may be associated with certain limitation because of short half life (45 hours) with risk of premature leutinization and suboptimal follicular development in some patient. the finite duration of treatment may limit its role in cases of persistent anovulation , recurrent infertility. The rationale behind use of extended regimn letrozole lies its ability to maintain low estrogen levels and sustain the inhibitory effect on aromatase enzyme activity throughout the follicular phase ,thereby promoting follicular growth and enhancing the likelihood of achieving a mature dominant follicle . By extending the duration of letrozole therapy beyond the conventional therapy, clinician can captilize on the cumulative effects on aromatase inhibition, potentially yielding higher ovulation rates and pregnancy outcomes, however this regimn is not without its challenges and considerations . Prolonged exposure may increases the risk of Ovarian hyper-stimulation syndrome or endometrial abnormlities. The optimal duration of extended regimn remains a subject of ongoing research in treatment protocols and outcomes across studies. So, with this background present study was conducted to compare the role of low dose-extended or long letrozozle protocol and double dose-short letrozole protocol in induction of ovulation in infertile patients with anovulatory cycles.

MATERIAL AND METHODS

This is a prospective comparative study comprising of 80 women with anovulatory cycles attending the gynaecology OPD in Department of Obstetrics and Gynaecology, of F.H.M.C. Etmadpur ,Agra from the period Jan 2023 to Dec 23

Inclusion Criteria

1. Age between 20-35 years with primary/ secondary infertility .
2. Normal hormonal profile (S.TSH, S.Prolactin, S.LH , S.FSH)
3. Normal HSG report.
4. Normal husband’s semen analysis .

Exclusion Criteria

1. Age of patient < 20 years, >35 years.
2. Patient with any type of fibroid, endometriosis.
3. Patient with history of any previous uterine surgeries.
4. Patient with tubal obstruction.

After full filling the inclusion criteria total number of participants divided in two group each having 40 participants.

Group A– Extended protocol 2.5mg/day X 10days (D1-D10 of menses).

Group B – Short protocol 5mg/day X 5days (D2-D7 of menses).

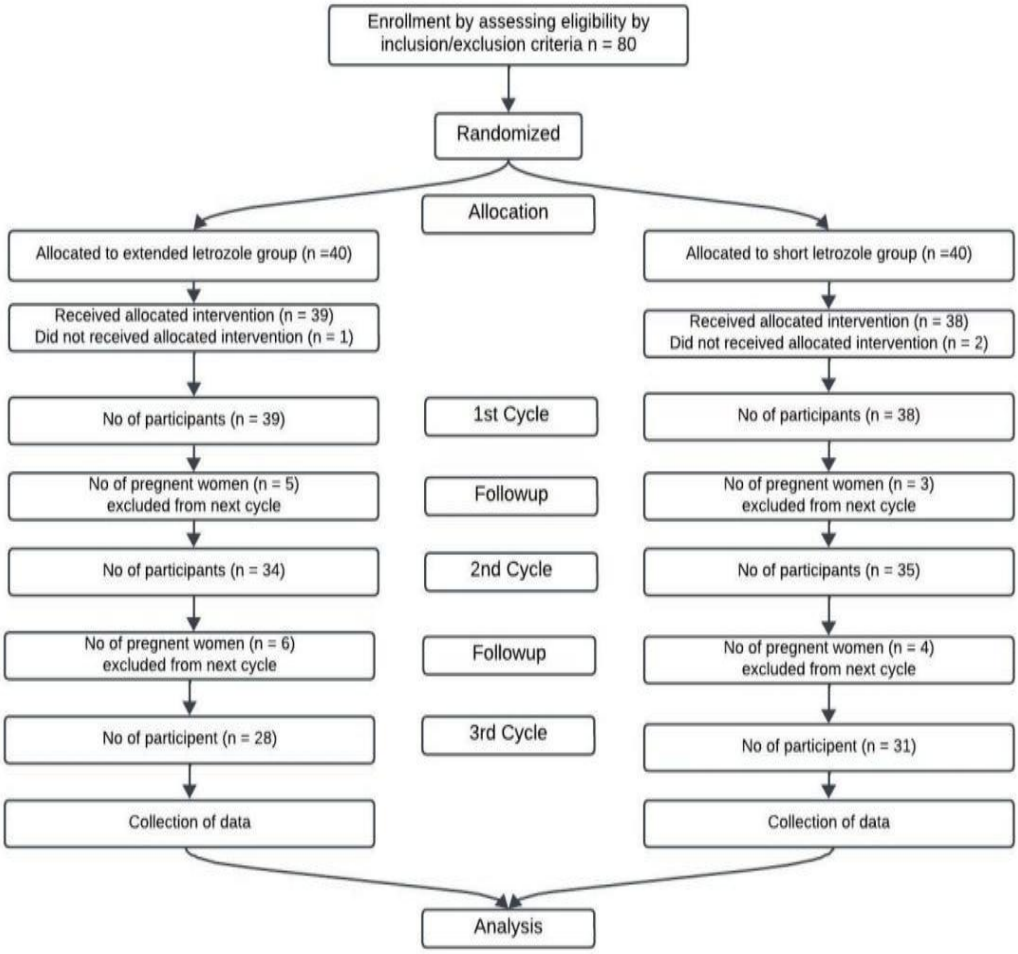
Patient were given Tab letrozole in short protocol from day2 -days7 of menstrual cycle and extended protocol be given Tab Letrozole day1-day10 of menstrual cycle. Patients were followed from day 11 of the menses for follicular monitoring via USG till dominant follicle become 18 mm in size. The size of the biggest follicle was measured during transvaginal sonography by taking the mean of the two greatest internal follicular diameters measured in two planes perpendicular to each other. Endometrial thickness was measured at the greatest diameter perpendicular to the mid sagittal plane in the fundal region.A trigger (injection Beta h CG 5000 iu) was given and patients were adviced for intercourse after 24-36 hrs of injection. They were then called after 16-18 days for urine pregnancy test. Primary outcome was monitored as Number of follicles >14mm, Number of follicles >18mm, Endometrial thickness at the time of Hcg injection. Secondary outcome was monitored as ongoing pregnancy defined as viable pregnancy of at least 12 weeks.

Statistical Analysis

Statistical analysis was performed using SPSS program version 20.0. Demographic data were expressed as percentage, mean (for parametric data) or median (for non-parametric data), and . Chi-square tests and relative risk for correlation were used for categorical variables. And independent t-test is used. For the purposes of this analysis, Chi-square tests were used for categorical variable.

RESULT

A total of 80 women were included in this study. And they were devided in two groups of 40 patients. In gp 1, 39 out of 40 took treatment while in gp 2, 38 out of 40 took the treatment.



As sown in table no 1 there is no significant difference in age group, and parity status(p=0.093,.303) in both group, while there is significant difference in BMI in both group.

Table 1: Baseline characteristics of study participants

Variables	Extended Letrozole group (n=39)		Short letrozole group(n=38)		p -value
	Frequency/mean± SD	percentage	Frequency/mean± SD	percentage	
Age	26.05±3.87		27.68±4.53		0.093
18-29	31	79..5	28		
≥30	8	20.5	10		
BMI (Kg/m^2)	21.95±2.28		22.73±2.61		0.00
18-24.99(normal)	34	87.2	31	81.6	
≥25(over weight)	5	12.8	7	18.4	
Type of infertility					0.303
Primary	21	53.8	16	42.1	
Secondary	18	46.2	22	57.9	

As shown in table no 2 there is no significant difference in hormonal profile of both group except in prolactin level (p value=.003)

Table 2: Hormone profile of study Participants

Variables	Extended Letrozole group (n=39) mean± S D	Short letrozole group(n=38) mean± S D	p- value
FSH((**mIU**/ml)	6.11± 1.007	5.95 ± 0.948	0.475
LH((**mIU**/ml)	6.47 ± 0.891	6.121 ± 0.8363	0.079
TSH(**mIU**/ml)	2.72 ±0.822	2.786 ± 0.7746	0.742
Prolactin(ng/ml)	15.70 ±2.54	17.31 ± 1.90	0.003

As shown in table no 3,there is no statistically significant difference Table 3: Total no of growing follicles in study Population were not significantly different in all 3 cycles

No of growing follicles	Extended letrozole group Frequency	percentage	Short letrozole group Frequency	percentage	p- value
1st cycle					
0	6	15.4	7	18.4	0.850
1	28	71.8	25	65.8	
>1	5	12.8	6	15.8	
2nd cycle					
0	6	17.6	6	17.6	0.659
1	24	70.6	24	70.6	
>1	4	11.8	4	11.8	
3rd cycle					
0	6	21.4	4	12.9	0.215
1	19	67.9	25	80.6	
>1	3	10.7	2	6.5	

As shown in table no 4 ,Size of follicle is given in all three cycles is comparable.

Table 4: Size of Follicles in study Population

Size of growing follicles	Extended letrozole group Frequency	percentage	Short letrozole group Frequency	percentage	p value
1st cycle					
14-18mm	33	84.6	30	81.1	0.569
>18mm	33	84.6	29	76.3	
2nd cycle					
14-18mm	24	70.6	24	70.6	0.031
>18mm	23	67.6	23	67.6	
3rd cycle					
14-18mm	19	67.9	26	83.8	0.041
>18mm	19	67.9	26	83.9	

As shown in table no 5 ,difference in ovulation rate is not statistically significant in both groups.

Table 5: Comparison of ovulation rate in study Population

Ovulation rate	Extended letrozole group Frequency	percentage	Short letrozole group Frequency	percentage	p value
1st cycle					
Yes	28	71.8	29	76.3	0.651
No	11	28.2	9	23.7	
2nd cycle					
Yes	23	67.6	25	71.4	0.733
No	11	32.4	10	28.6	
3rd cycle					
Yes	19	67.0	22	71	0.796
No	9	32.1	09	29	

As shown in table no 6, difference in endometrial thichkness is statistically significant in 1st cycle in extended group.

Table 6: Comparison of Endometrial thickness in study population

Endometrial Thickness	Extended letrozole group Mean± SD	Short letrozole group Mean ±SD	p value
1st cycle	7.86±1.20	6.94±1.34	0.002
2nd cycle	7.67±1.46	7.72±1.14	0.898
3rd cycle	7.68±1.20	7.77±1.07	0.757

As shown in table no 7 there is no statistically significant difference in pregnancy rate in both group

Table 7: Comparison of pregnancy rate in study Population

Pregnancy rate	Extended letrozole group Frequency	percentage	Short letrozole group Frequency	percentage	p value
1st cycle					
Yes	5	12.8	3	7.90	0.479
No	34	87.2	35	92.1	
2nd cycle					
Yes	6	17.6	4	11.4	0.463
No	28	82.2	31	88.6	
3rd cycle					
Yes	5	17.9	4	12.9	0.597
No	23	82.1	27	87.1	

As shown in table no 8, there is no statistically significant differnace but short protocol is associated with abdominal pain.

Table 8: Adverse effect of Letrozole

Variables	Extended letrozole group Frequency	percentage	Short letrozole group Frequency	percentage	p value
1st cycle					
No effect	36	92.3	35	92.1	0.721
Headache	2	5.1	1	2.6	
Hot flushes	1	2.6	1	2.6	
Abdominal pain	0		1	2.6	
2nd cycle					
No effect	32	94.1	31	88.6	0.721
Headache	1	2.9	2	5.7	
+++Hot flushes	1	2.9	1	2.9	
Abdominal pain	0		1	2.9	
3rd cycle					
No effect	26	92.9	28	90.3	0.820
Headache	1	3.6	1	3.2	
Hot flushes	1	3.6	1	3.2	
Abdominal pain	0		1	3.2	

DISCUSSION

This study suggest that extended letozole therapy shows more no of growing follicles, more ovulation rate ,more no of pregnancy but data is not statistically significant.In our study, mean age of extended letrozole group (group I) was 26.05±3.87 years and that of short letrozole group (group II) was 27.68±4.53 years (Table 1). There was no significant difference between two groups. Similar age group patients were selected by Badawy[9] and Hassanein[10].Mean body mass index (BMI) was 21.95±2.28 kg/m2 in group I and 22.73±2.61kg/m2 in group II in our study which was more or less normal BMI. There was no significant difference between two groupgroup had more primary infertility than secondary whilein short group patients had more secondary infertility than primary. The study participants were normogonadotropic in the present study with no significant difference between two groups (Table 2). The mean LH levels were around 6.47mIU/ml in Extended and 6.1mIU/ml Short letrozole group. respectively.There is statistically significant difference in prolactin level in both groups(p=.003).

Badawy et al, Hassanein et al, Yadav P[11] et al, Aziz et al[12], and Salama[13] et al.conducted few recent RCTs on extended use of letrozole for ovulation induction in patients with polycystic ovary syndrome by 18,23-26 These studies demonstrated better results in terms of multifollicular development, increased size and number of mature follicle, ovulation and pregnancy rate than traditional short letrozole protocol, and the

results are similar to our study, but statistically not significant In this present study, pregnancy occurred in 16 out of 39 patients in extended letrozole group and in 11 out of 38 patients in short letrozole group (Table 7). Comparing two groups, it was manifested that pregnancy rate was somewhat higher in group I (41.02%) than group II (28.9%). However, cumulative pregnancy rate between two groups were not significant statistically. This result came in parallel with Badawy et al (17.4% versus 12.4%; p value-0.03), Aziz et al (20% versus 13.3%), Salama et al (25% versus 15%), Hassanein et al (24% versus 14%) and Yadav et al (18.3% versus 12.5%) studies that displayed higher pregnancy rate either cumulative or per cycle in extended letrozole group than the other.

CONCLUSION

It was accepted that by extending the letrozole therapy in midfollicular phase would maintain the FSH window prolonged allowing multifollicular developement. this extended protocol appears to be more effective than the conventional short protocol with more no of matured follicles and more clinical pregnancy rate. However large randomized controlled trials are needed to establish standard regimn for ovulation induction.

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Conflict of interest: No

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