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Original Research Article

Effect of estradiol valerate on endometrial thickness in polycystic ovary syndrome having ovulation induction with letrozole

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ABSTRACT

Background: PCOS is a common endocrine disorder in women of reproductive age. Letrozole is an orally active aromatase inhibitor and as effective as chlomiphene citrate for induction of ovulation. Estrogen is important in the regeneration and growth of the endometrium prior to ovulation prepare the tissue to respond to progesterone post ovulation in PCOS patients. Aim of the study was to assess the effects of estradiol valerate on endometrial thickness in PCOS having ovulation induction with letrozole.
Methods: This randomized controlled study was conducted in the department of reproductive endocrinology and infertility, BSMMU, Dhaka, with 1 year duration. A total 80 diagnosed cases of PCOS patients with subfertility were included in this study. Among them 40 patients received letrozole and estradiol valerate and 40 patients received letrozole and placebo.
Results: On day 8, mean endometrial thickness was not statistically significant between two groups (p=0.436). On day of triggering, mean endometrial thickness was significantly higher in intervention group 9.2±1.4 mm than control group 8.2±1.4 mm (p=0.004). Mean changes of endometrial thickness on day of triggering compared with on day 8 was significantly higher in intervention group 3.2±1.5 mm than control group 2.5±1.6 mm (p=0.043). Pregnancy rate was higher in intervention group 13 (38.2%) than control group 8 (22.2%) with relative risk 1.72, 95% CI (0.82-3.63%), that was not statistically significant between two groups (p=0.144).
Conclusions: Mean changes of endometrial thickness on day of triggering were significantly higher in intervention group than control group. The pregnancy rate achieved with letrozole+estradiol valerate combination was higher than that achieved with letrozole and placebo group.

Keywords: Endometrial thickness, Estradiol valerate, Letrozole

INTRODUCTION

The polycystic ovary syndrome (PCOS) is the most frequent multisystem endocrinopathy among women of reproductive age. It is generally accompanied by reproductive complications importantly infertile which accounts for around 6-21%.[1] The current incidence of PCOS (5-6%) is increasing fast due to psychological and physical stress and change in lifestyle. It has also become a common problem among adolescent girls developing soon after the puberty.[2] Identifying the main causes of infertility to plan appropriate treatment is diagnostic and therapeutic priority.[3] Among different drugs, clomiphene citrate is frequently used for ovulation induction. According to the previous studies, the success of pregnancies was less than expected, with CC between 25-43%.[4] Letrozole is found equally effective as clomiphene citrate for induction of ovulation in patients with PCOS.[5] Many researchers have studied this drug as one of the best options for ovulation induction in PCOS.[6] After giving the ovulation inducing drugs, the reduced fertility is apparently attributed not only due to anovulation but also

for endometrial dysfunction in patient with PCOS. So, to improve the endometrial functions is of potential therapeutic targets to increase the appropriate outcome of women with PCOS. Letrozole usually act locally in the ovary through increasing intra-ovarian androgens (due to blockage of its conversion to estrogen), resulting in lower level of circulating estrogens which stimulates the pituitary to produce more FSH by negative feedback. The higher level of circulating FSH as well as the increase in follicular androgen causes enhanced follicular sensitivity and growth. The endometrial thickness is one of the most important factors for implantation. If the endometrial thickness is less than 6-8 mm the pregnancy rate can be very low.[7] Khanna showed that ethynyl estradiol is used to treat protocols that include clomiphene citrate produce a favourable endometrial response in infertile women with PCOS.[8] Estradiol valerate is a synthetic estrogen and hence is an agonist of the estrogen receptor, the biological target of estrogens like estradiol. This natural and bioidentical form of estrogen is an FDA approved drug and have some benign side effect like bloating, nausea, breast tenderness, oedema, headache etc.[9] A double blind clinical trial reported that, controlled use of letrozole increased endometrial thickness and pregnancy rate than estradiol valerate and clomiphene citrate in infertile especially, in PCOS women.[10] The first letrozole treatment with estradiol valerate in PCOS pt was randomized controlled study which was designed and shown that endometrial thickness and pregnancy rate is significantly higher in letrozole/estradiol valerate combination than with letrozole alone.[11] So, the aim of the study was to find the most effective drug or drugs combination especially use of estradiol valerate to improve the endometrial thickness in infertile women with PCOS.

Objectives

General objective

To assess the effects of estradiol valerate on endometrial thickness in PCOS having ovulation induction with letrozole.

Specific objectives

To measure the endometrial thickness on day 8 having ovulation induction with letrozole. To compare the endometrial thickness on day 8 and on the day of triggering in both groups.

METHODS

This randomized controlled trial study was carried out in the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. From January 2022 to December 2022 (1 year). The study population was the subfertile women with PCOS having ovulation induction with letrozole (ET<7 mm on day 8 by TVS) attending out-patient department fulfilling the inclusion and exclusion criteria. About 80 patients with endometrial thickness <7 mm and follicular size >10 mm was selected and randomized into intervention group (letrozole and estradiol valerate) 40 patients and control group (letrozole and placebo group) 40 patients by permuted block randomization using computer generated random table. Written approval was taken from the concerned authority and the department with due procedure as well as the patients were explained in detail regarding the objectives, rationality and potential benefits of the study. The patients were counselled regarding the drugs and unexpected side-effects and an informed written consent was taken. Infertile PCOS patients were enrolled in this study. They were given tablet letrozole 2.5 mg 2 tab daily from day 3 to day 7 of menstruation after the baseline visit and investigations. Folliculometry was done on day 8 with TVS and endometrial thickness was noted. Tab estradiol valerate 4 mg (1 mg 2 tablets twice daily) for 5 days from day 8 of menstrual cycle or withdrawal bleeding up to day 12 for intervention group and placebo was given from day 8 to day 12 for control group. Then folliculometry by TVS was done on 12th day and endometrial thickness was measured. Folliculometry was repeated every 1-3 days interval until mean follicular diameter reaching ≥18 mm and endometrial thickness was measured. If follicular size was not satisfactory, they were excluded from the study. Injection HCG 5000 IU was given to women with follicular size ≥18 mm and timed intercourse was advised every other day from the day of HCG administration. Patient was advised for doing pregnancy test at least 14 days after triggering either by pregnancy test kit or by β-HCG estimation for confirmation of pregnancy as per patient's convenience. For each and every subject separate data collection sheet was prepared. Data was collected from the patients on different visits on variables of interest using interview, observation, clinical examination, investigations and from the history sheet of the patients. Data was collected through interview, physical examinations, laboratory investigations and TVS. All the data was enrolled in the data sheet for this study. Statistical analysis was carried out by using SPSS version 23.0.

Inclusion criteria

Age 18 to 40 years. Diagnosed case of PCOS patients with subfertility. Endometrial thickness is <7 mm on day 8 by TVS after ovulation induction by tablet letrozole (5 mg day 3 to day 7 of menstruation).

Exclusion criteria

BMI<18 and >30 kg/m^2. Women having bilateral tubal block. Male partner having abnormal semen parameter. Size of the follicles <10 mm in size in day 8. Patient having hypothyroidism and hyperprolactinaemia.

RESULTS

A total of 80 diagnosed cases of PCOS patients with subfertility were included in this study maintaining

inclusion and exclusion criteria. Among them 40 patients received letrozole and estradiol valerate (intervention group) and 40 patients received letrozole and placebo (control group). We found the majority participants 36 (90%) in intervention group and 28 (70%) in control group belonged to age group 21-30 years mean age 25±3.2 and 23.9±3.7 respectively. Most of the patients were primary subfertility in both groups, that was 32 (80%) in intervention group and 31 (77.7%) in control group. Their found maximum participants BMI (body mass index) was 25.0-29.9 which indicates overweight, about 27 (67.5%) in intervention group and 25 (62.5%) in control group were found. There was no statistically significant difference between two groups (p>0.05) regarding age, type of infertility, duration of infertility and BMI (Table 1).

Table 1: Socio-demographic characteristics of study population (N=80).

Demographic characteristics	Intervention group (letrozole and estradiol valerate) (n=40)		Control group (letrozole and placebo) (n=40)		P value
	n	%	n	%	
Age (years)					
18-20	3	7.5	8	20	
21-30	36	90	28	70	
31-40	1	2.5	4	10	
Mean±SD	25±3.2		23.9±3.7		0.146
Range (min-max)	18-36		18-34		
Type of infertility					
Primary	32	80	31	77.5	0.785
Secondary	8	20	9	22.5	
Duration of infertility (years) (mean±SD)	3.6±1.9		3.3±2.2		0.454
Range (min-max)	1	-10	1	-12	
BMI (kg/m^2)					
18.5-24.9	13	32.5	15	37.5	
25.0-29.9	27	67.5	25	62.5	
Mean±SD	25.7±2.2		25.8±2.4		0.854
Range (min-max)	21.9-29.8		21.4-29.5		

Table 2: Baseline biochemical parameter of study population (N=80).

Parameter	Intervention group (letrozole and estradiol valerate) (n=40)	Control group (letrozole and placebo) (n=40)	P value
	Mean±SD	Mean±SD	
Serum FSH (mIU/ml)	5.5±1.8	5.9±1.8	0.247
Serum LH (mIU/ml)	6.9±3.5	6.5±3.4	0.639
LH/FSH ratio	1.38±0.81	1.18±0.68	0.247
Serum testosterone (ng/dl)	46.8±23.8	46.7±22.8	0.992

Table 3: The folliculometry follow up of the study population of menstruation (N=80).

Folliculometry on different follow-up	Intervention group (letrozole and estradiol valerate)	Control group (letrozole and placebo)	P value
	Mean±SD	Mean±SD	
On day 8 of menstruation (n=80)	40	40	
Number of follicles	2.1±1.0	1.7±0.9	0.064
Size of follicle (mm)	12.4±2.1	12±2.4	0.482
Endometrial thickness (mm)	5.9±0.9	5.8±0.9	0.436
On day 12 of menstruation (n=76)	38	38	
Largest follicle size (mm)	19.13±4.1	18.9±3.9	0.491
Number of dominant follicles	1.58±0.97	1.46±0.58	0.588
On day triggering			
Largest follicle size (mm) (Mean±SD)	19.17±1.05	19.23±0.56	0.896
Number of dominant follicles (Mean±SD)	1.2±0.42	1.25±0.46	0.814

Table 4: Endometrial thickness of study population on day 12 and day of triggering.

Endometrial thickness (mm)	Intervention group (letrozole and estradiol valerate)		Control group (letrozole and placebo)		P value
	N	%	N	%	
On day 12	**(n=38)**		**(n=38)**		
<7	1	2.6	9	23.7	
≥7	37	97.4	29	76.3	
Mean±SD	9±1.5		7.7±1.2		0.001
On day of triggering	**(n=34)**		**(n=36)**		
<7	0	0	5	13.9	
≥7	34	100	31	86.1	
Mean±SD	9.2±1.4		8.2±1.4		0.004

Table 5: Endometrial thickness in different follow up.

Endometrial thickness (mm)	Intervention group (letrozole and estradiol valerate)	Control group (letrozole and placebo)	P value
	Mean±SD	Mean±SD	
On day 8 (n=80)	5.9±0.9	5.8±0.9	0.436
On day of triggering (n=70)	9.2±1.4	8.2±1.4	0.004
P value (on day 8 vs day of triggering)	0.001	0.001	
Change on day of triggering	3.2±1.5	2.5±1.6	0.043

Table 6: Pregnancy rate in both groups.

Pregnancy rate	Intervention group (letrozole and estradiol valerate)		Control group (Letrozole and placebo)		RR (95%CI)	P value
	(n=34)		(n=36)			
	n	%	n	%		
Pregnant	13	38.2	8	22.2	1.72	0.144
Non pregnant	21	61.8	28	77.8	(0.82-3.63)	

The mean serum FSH, LH, LH/FSH ratio and serum testosterone were not statistically significant (p>0.05) between two groups (Table 2). The mean of on day 8 of menstruation of 80 study patients (intervention group n=40 and control group n=40) number of follicle 2.1±1.0 and 1.7±0.9, size of follicle 12.4±2.1 and 12±2.4, endometrial thickness 5.9±0.9 and 5.8±0.9 found in intervention group and control group respectively. On day of triggering 76 study patients (intervention group n=38 and control group n=38) as two cases dropout in intervention group and control group respectively mean follicle size was 18.3±4.1 mm and 18.9±3.9 mm, mean number of dominant follicles was 1.58±0.97 and 1.46±0.58 in intervention and control group respectively. Mean follicle size was 19.17±1.05 mm in intervention group and 19.23±0.56 mm in control group. Mean number of dominant follicles was 1.20±0.42 and 1.25±0.46 in intervention and control group respectively. There was no statistically significant difference between two groups (p>0.05) (Table 3). On day 12, endometrial thickness ≥7 mm was higher in intervention group 37 (97.4%) than control group 29 (76.3%). Mean endometrial thickness was significantly higher in intervention group than control group 9.0±1.5 mm and 7.7±1.2 mm. On day of triggering endometrial thickness ≥7 mm was higher in intervention group than control group 34 (100.0%) 31 (86.1%). Mean endometrial thickness was significantly higher in intervention group than control group 9.2±1.4 mm and 8.2±1.4 mm. The point to be noted that 4 cases in intervention group and 2 cases in control group were excluded from the study because follicular size did not reach 18 mm (Table 4). On day 8, a total 80 study patients (intervention group n=40 and control group n=40), mean endometrial thickness was not statistically significant between two groups (p=0.436). Mean changes of endometrial thickness on day of triggering compared with on day 8 was significantly higher in intervention group 3.2±1.5 mm than control group 2.5±1.6 mm (p=0.043) (Table 5). Pregnancy rate was higher in intervention group 13 (38.2%) than control group 8 (22.2%) with relative risk 1.72, 95% CI (0.82-3.63%), that was not statistically significant between two groups (p=0.144) (Table 6).

DISCUSSION

Polycystic ovarian syndrome is the most common endocrine disorder responsible for subfertility among the reproductive age women.[12] Letrozole which is an aromatase inhibitor, has been explored as a superior

alternative by many researchers, but the evidence about its efficacy as compared to clomiphene is still conflicting.[13] During ovulation induction, the positive effect of estradiol valerate on the endometrial thickness has been proven in many literatures. In the study of Satirapod et al.[14] They found that addition of estradiol valerate in a dose of 6 mg/day from 10 to 14 days of the menstrual cycle in patients induced by clomiphene citrate significantly increased endometrial thickness, that comparison with patients who received clomiphene citrate alone.

This study showed majority participants belonged to age group 21-30 years in both groups. The mean age difference was not statistically significant between two groups (p=0.146). Most of the patients were primary subfertility in both groups, that was 80.0% in intervention group and 77.7% in control group, the difference was not statistically significant (p=0.785). Mean duration of infertility and BMI were not statistically significant (p>0.05) between two groups. This was similar to the findings of the studies conducted by Alnemr et al and Sarhan et al.[11,15]

The present study found the mean serum FSH, LH, LH/FSH ratio and serum testosterone were not statistically significant (p>0.05) between two groups. In a study done by Sarhan et al.[15] had observed that mean FSH and LH were not statistically significant between two groups.

In this study it was observed that in baseline folliculometry on day 8 of menstruation, mean number of follicles, mean size of follicle and endometrial thickness were not statistically significant between two groups (p>0.05). In a randomized double blind clinical trial study done by Seyedoshohadaei et al where they included 100 women with PCOS, patients were divided into two groups, group A received 100 mg clomiphene citrate from day 3 to day 7 of menstruation and 4 mg estradiol valerate after the 8th day of menstruation until 14th day and group B treated by 5 mg letrozole from day 3 to 7 of menstruation with placebo from 8th to 14th day of menstruation.[10] They observed in baseline folliculometry the mean of endometrial thickness in group A (clomiphene- estradiol valerate) and B (letrozole) before the intervention were 5.34 and 5.68 mm respectively. There was no significant difference between two groups statistically (p=0.174).

The mean of on day 8 of menstruation of 80 study patients (intervention group n=40 and control group n=40) number of follicles 2.1±1.0 and 1.7±0.9, size of follicle 12.4±2.1 and 12±2.4, endometrial thickness 5.9±0.9 and 5.8±0.9 found in intervention group and control group respectively. On day of triggering 76 study patients (intervention group n=38 and control group n=38) as two cases dropout in intervention group and control group respectively mean follicle size was 18.3±4.1 mm and 18.9±3.9 mm, mean number of dominant follicles was 1.58±0.97 and 1.46±0.58 in intervention and control group respectively. Mean follicle size was 19.17±1.05 mm in intervention group and 19.23±0.56 mm in control group. Mean number of dominant follicles was 1.20±0.42 and 1.25±0.46 in intervention and control group respectively. There was no statistically significant difference between two groups (p>0.05). In a randomized controlled study conducted by Alnemr et al, where they included 273 patients who underwent ovulation induction and timed intercourse.[11] Patients were divided into 2 groups: controlled ovarian stimulation was done in group 1 by letrozole with addition of estradiol valerate and in group 2 by letrozole alone. They found that the number of cases reaching mature follicular size during the study period, there was no statistically significant differences (p>0.05) between the 2 studied groups (61.1% compared to 60.4%).

On day 12, endometrial thickness ≥7 mm was higher in intervention group 37 (97.4%) than control group 29 (76.3%). Mean endometrial thickness was significantly higher in intervention group than control group 9.0±1.5 mm and 7.7±1.2 mm. On day of triggering endometrial thickness ≥7 mm was higher in intervention group than control group 34 (100.0%) 31 (86.1%). Two studies on ET and continuing pregnancy compared infertile patients with ET measurements of less and more than 9 mm and found a significantly higher rate of continuing pregnancy in those with an ET more than 9 mm.[16] El-Toukhy et al have reported that both very thin (<7 mm) and very thick (>14 mm) endometrium have an adverse effect on implantation, with the highest pregnancy rates being seen in patients with an ET between 9 and 14 mm, that support with my study.[17]

Mean endometrial thickness was significantly higher in intervention group (letrozole plus estradiol valerate) than control group 9.2±1.4 mm and 8.2±1.4 mm, which was better than clomiphene plus estradiol valerate group. In a randomized double-blind study obtained by Harira, in their study a total of 172 women unexplained infertility with improper endometrial response to CC in spite of good follicular response were included in the study.[18] They observed that endometrial thickness was increased after administration of estradiol valerate to CC from (5.44±1.64) to (8.28±1.7) or letrozole alone (5.75±1.92) to (9.2±1.8) to unexplained infertile patients, with significant difference between the two groups (p<0.00). In letrozole group endometrial thickness was higher than CC plus estradiol valerate. The above studies by Seyedoshohadaei et al, Sarhan et al, by Harira, showed that letrozole increase endometrial thickness more than the estradiol valerate and clomiphene citrate.[10,15,18] In those studies, mean endometrial thickness of clomiphene plus estradiol valerate group were (7.26±1.7), (8.8±1.2), and (8.28±1.7) respectively. Roy et al revealed that the mean midcycle trilaminar layer of endometrial thickness in the letrozole group was 9.1±0.3 mm compared with 6.3±1.1 mm in CC group, which was statistically significant (p=0.014).[19] In a study by Satirapod et al the effects of estradiol valerate on the thickness of clomiphene citrate-stimulated endometrium was examined and they concluded that the administration of estradiol valerate following the clomiphene citrate treatment can prevent the endometrial thinning that was similar to our study.[14]

Pregnancy rate was higher in intervention group 13 (38.2%) than control group 8 (22.2%) with relative risk 1.72, 95% CI (0.82-3.63%), that was not statistically significant between two groups (p=0.144). In a study conducted by Alnemr et al included 273 patients who underwent ovulation induction and timed intercourse, also there were divided into 2 groups: controlled ovarian stimulation was done in group 1 by letrozole with addition of estradiol valerate and in group 2 by letrozole alone.[11] The study showed clinical pregnancy rate was significantly higher in the group of patients receiving combined letrozole+estradiol valerate rather than the group of receiving letrozole alone (24.4% versus 11.9%), that was not support with this study. This may be explained by the small sample size in our study. Estradiol valerate have a positive effect on endometrial receptivity and the quality of cervical mucus. Letrozole alone may create an estrogen deficient environment for a short time which may last for 45 hours during the time of ovulation.[20] The pregnancy rate in the letrozole group was almost twice as clomiphene plus estradiol valerate group and the difference was significant (32.0% versus 16.0%), that was not correlated with my study due to letrozole had a better effect on endometrial thickness and endometrial response and pregnancy rate compared with clomiphene citrate.

This randomized controlled trial study carried out through a small sample size as well as in a short period. For being a study in a single community with comparatively small number of sample size, the study result may not reflect the exact scenarios of the mass people.

CONCLUSION

In conclusion, the present study provides the evidence showing that intervention group (letrozole and estradiol valerate) supplementation resulted in endometrial thickness ≥7 mm on day of trigging were significantly higher than control group (letrozole and placebo). However, mean changes of endometrial thickness on day of triggering were significantly higher in intervention group than control group. So letrozole plus estradiol valerate increased the endometrial thickness significantly as compared to letrozole plus placebo in infertile PCOS patients who had improper endometrial thickness. The pregnancy rate achieved with letrozole+estradiol valerate combination was higher than that achieved letrozole and placebo group. However, mean changes of endometrial thickness on day of triggering were significantly higher in intervention group than control group. Future studies with longer duration of the intervention and bigger sample size are needed to confirm the validity of our findings. Multiple centers can be included to support current conclusions. Comparison of estradiol valerate with other drugs like sildenafil, aspirin, vitamin E can be done in future studies.

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