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A comparative study to evaluate the efficacy of Letrozole and Clomiphene Citrate for ovulation induction in sub fertile women

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Abstract:
Background: *Ovulation induction is a treatment option for subfertility that can be achieved through medication. In this study, the efficacy of Letrozole and Clomiphene citrate on ovulation induction in women were compared.*
Materials and Methods: *In this prospective randomized study, a total of 62 patients were treated with Letrozole and clomiphene citrate. Out of which, 31(50%) patients are treated with Letrozole and categorized into group A and 31 (50%) patients were treated with clomiphene citrate, categorized into group B. Overall, 173 cycles were studied and followed up in 62 patients [85 cycles in Letrozole patients (group A) and 88 cycles in Clomiphene Citrate patients (group B)]. In both groups, the parameters like age, diagnosis, baseline level hormones and side effects were compared.*
Results: *In a total of 62 patients, ovulation was observed during the period of study among 27 (43.5%) patients receiving Letrozole and 20 (32.2%) patients in Clomiphene citrate group. Therefore, Letrozole is more involved in ovulation than clomiphene.*
Conclusion: *Letrozole shows effectiveness in follicular diameter and endometrial thickness in patients with subfertility compared to clomiphene. In addition, the rate of ovulation is higher in Letrozole than clomiphene.*
Key words: *Ovulation induction; subfertility; Letrozole; Clomiphene Citrate.*

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I. Introduction

The terms Subfertility and Infertility are often used interchangeably. Subfertility is typically defined as any form of diminished fertility with a prolonged period of unwanted non-conception. Infertility is a condition characterized by the inability to conceive even after 12 months of normal and unregulated coitus to achieve pregnancy. Ovulation induction is the process by which medicines are used to stimulate the ovulation process in women with irregular (oligo ovulation) or absent ovulation (anovulation) [1][2]. The goal of ovulation induction is to increase the chance of conceiving naturally or by other fertility treatment. Ovulation disorders constitute approximately 30 to 40 percent of all instances of female infertility. Most of the causes of subfertility are same as infertility. Both male and female are equally responsible for causes. Some of the causes of subfertility in female are Anovulatory Infertility, Polycystic ovaries, Endometriosis, Ovarian dysfunction. Clomiphene citrate (clomid, Serophene) has been the traditional first line medical treatment for ovulation induction in infertile patients. The primary remedy for PCOS for many years has been the clomiphene citrate (CC) [2][4]. It binds to estrogen receptors and protects the hypothalamus from negative feedback. Letrozole is an alternative to Clomiphene citrate. The risk of spontaneous miscarriage in the Letrozole treated women is at lower rate. Currently, Letrozole has shown better results, with higher ovulation rates and pregnancy rates. Letrozole is an aromatase inhibitor which increases estradiol synthesis by reducing the conversion of androgen to estradiol in granulosa cells[6]. IUI may be offered to those who do not ovulate with OI but fail to achieve pregnancy after 6 months of treatment.

II. Materials and Methods

Institution of study: This study was conducted in the department of Obstetrics & Gynecology, Durgabai Deshmukh Hospital and Research Centre, Vidya nagar, Hyderabad.
Study duration: This study is proposed to be conducted for 6 months.
Study design: Prospective Randomized Comparative Observational study.
Sample size: 62, which are randomly categorized into two groups. Group-A: 31 subjects receiving clomiphene citrate. Group-B: 31 subjects receiving Letrozole.

Tool: patient case reports, Lab investigation reports.
Inclusion criteria: Patients of age group 18-35 years diagnosed with infertility or sub fertility with or without PCOS Patients with BMI≤35.
Exclusion criteria: Patients of age above 35 years. Patients with BMI ≥35, BMI <18 Infertility caused due to male factors.
Dose and duration: Letrozole and Clomiphene Citrate were prescribed orally once daily for 5 days from day 2 to day 4 of the menstrual period. - The initial dosage is one tablet (letrozole-2.5mg, Clomiphene Citrate- 50 mg) per day.

Procedure methodology:

After obtaining the consent from the patients, they were accounted in to the study. The study procedure was explained briefly signing in the informed consent form. The study was conducted after informed written consent is taken from the patient in all groups under of the guidance of a gynecologist in the hospital. The study was conducted by assessing the endometrial thickness, follicular size and the rate of ovulation among the patients visited to the outpatient department at Durgabai Deshmukh Hospital. Demographic data is collected from the patient case report. Patient medical history was taken. Clinical and biochemistry laboratory investigations were assessed. Efficacy of Letrozole and Clomiphene Citrate were studied. The results obtained were analyzed by one-way ANOVA.

Statistical analysis:

Data was analyzed using ANOVA, One-way analysis of variance that analyses data for both the groups. One –way Anova (Variance Analysis) is the widely used method of comparing measurement data group means. The basic principle is to calculate the mean of findings in each group and then compare the average difference in each group. Consequently, the test statistics are the measure of the difference between means separated by the average variance within groups. After a one-way anova, Tukey-Kramer test is the most commonly used post-hoc test. The minimum significance difference (MSD) for each pair of means is determined in this process[21].

III. Results

Ovulation was observed during the period of study among 27 (43.5%) Letrozole patients and in 20 (32.2%) clomiphene citrate groups. On day 17 of cycle an average follicular diameter was 20.90±5.43 mm (range 18-25 mm) in Letrozole and 18.45±7.31 mm in citrate clomiphene. On day 17 of the menstrual cycle, endometrial thickness was high with 12.34±3.53 mm in the Letrozole group and 10.76±4.09 mm in the citrate clomiphene group. In the clomiphene group, mean serum AMH levels were marginally higher (4.61±1.65 ng / ml) than in the Letrozole group (4.42±1.63 ng / ml). 27 patients were conceived from a group of Letrozole and 20 were conceived from a group of citrate clomiphene.

Table no 1 Shows patients diagnosed with subfertility when compared to other groups, age group 24-30(64%) are found to be more and age group 31-35(26%) and 18-23(10%) are less.

Table no 1: Shows number of patients diagnosed with subfertility according to age.

AGE IN YEARS	NO. OF PATIENTS	PERCENTAGE
18-23	6	10%
24-30	40	64%
31-35	16	26%

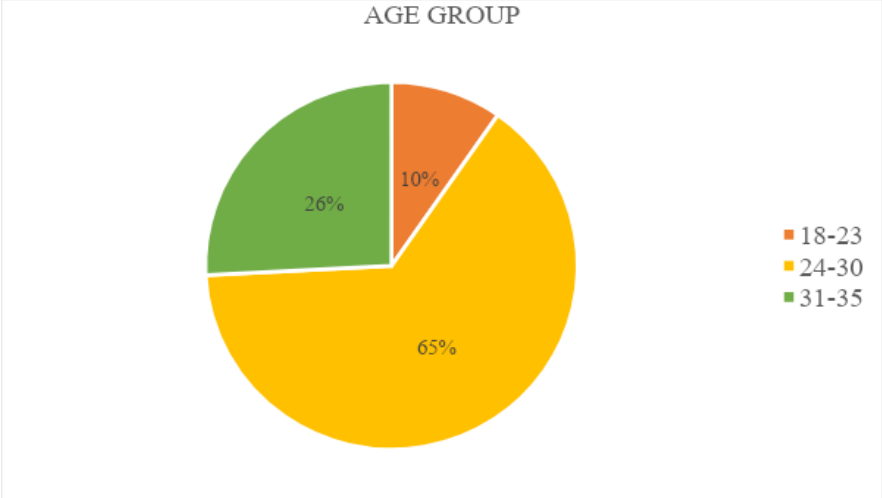


Table no2 records the Percentage of subfertile patients with comorbidities. Out of 62 patients diagnosed with subfertility, patients with risk factor co-morbidities were diabetes mellitus 2(14%), hypertension 1(7%), hypothyroidism 10(70%), pcos 5(28%).

Table no2: records the Percentage of subfertile patients with comorbidities.

CO-MORBIDITIES	NO. OF PATIENTS	PERCENTAGE
DIABETES MELLITUS	2	14%
HYPERTENSION	1	7%
HYPOTHYROIDISM	10	70%
PCOS	5	28%

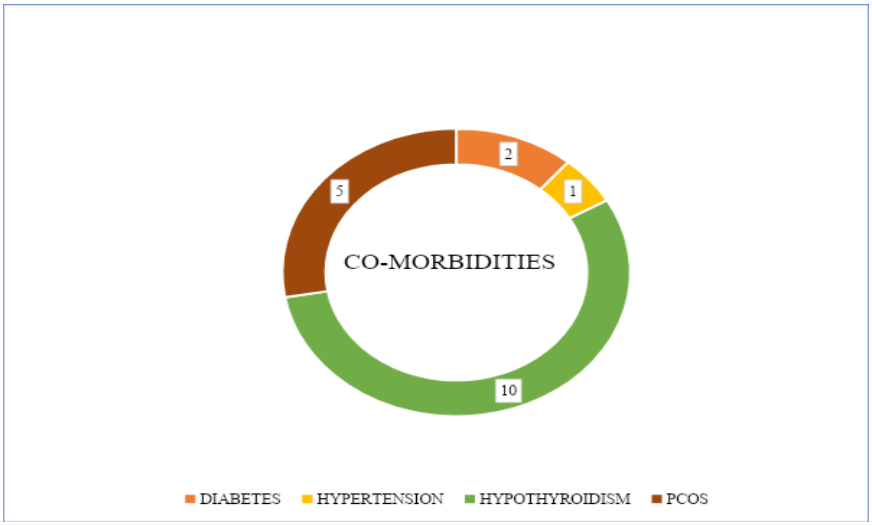


Table no3 Shows Percentage of patients prescribed with Letrozole and clomiphene citrate. Out of 62 patients with subfertility, total number of patients prescribed with letrozole are 31(50%) and clomiphene citrate are 31(50%).

Table no3: Shows Percentage of patients prescribed with Letrozole and clomiphene citrate

DRUG	FREQUENCY	PERCENTAGE
LETROZOLE	31	50%
CLOMIPHENE	31	50%

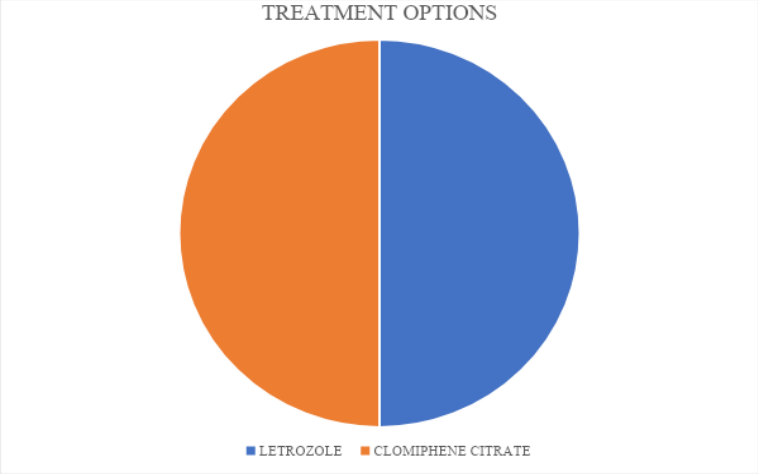


Table no4: Shows the number of patients conceived and not conceived during a five cycle therapy with Letrozole.

DRUG	CYCLES	VARIABLES	NO. OF PATIENTS
LETROZOLE	CYCLE 1	CONCEIVED	5
		NOT CONCEIVED	2
	CYCLE 2	CONCEIVED	8
		NOT CONCEIVED	1
	CYCLE 3	CONCEIVED	6
		NOT CONCEIVED	0
	CYCLE 4	CONCEIVED	4
		NOT CONCEIVED	0
	CYCLE 5	CONCEIVED	3
		NOT CONCEIVED	2

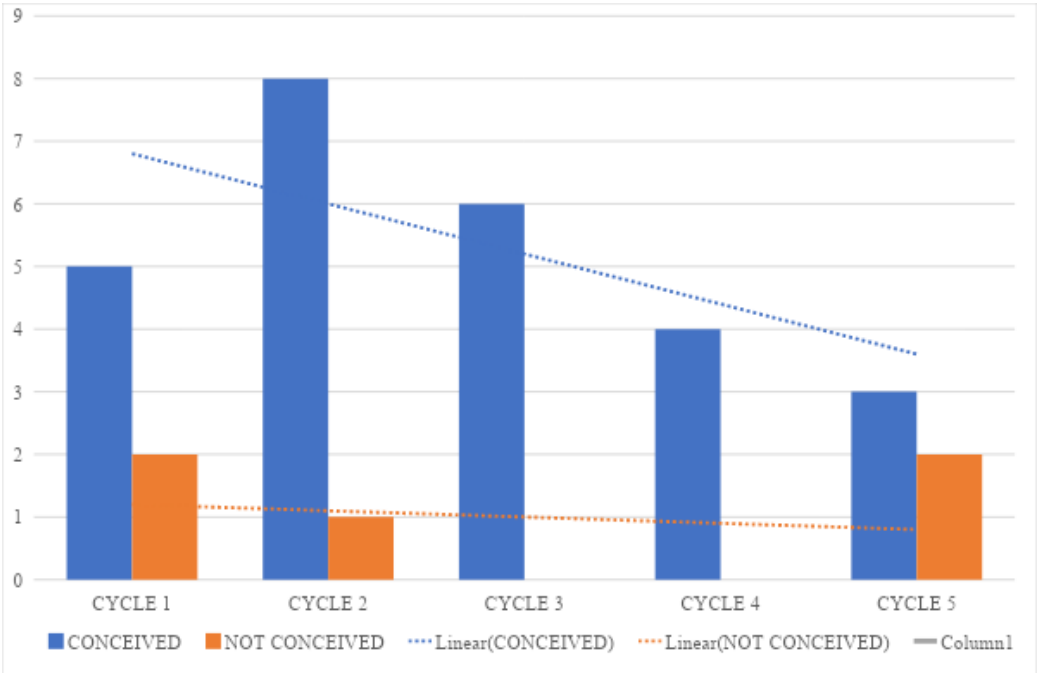
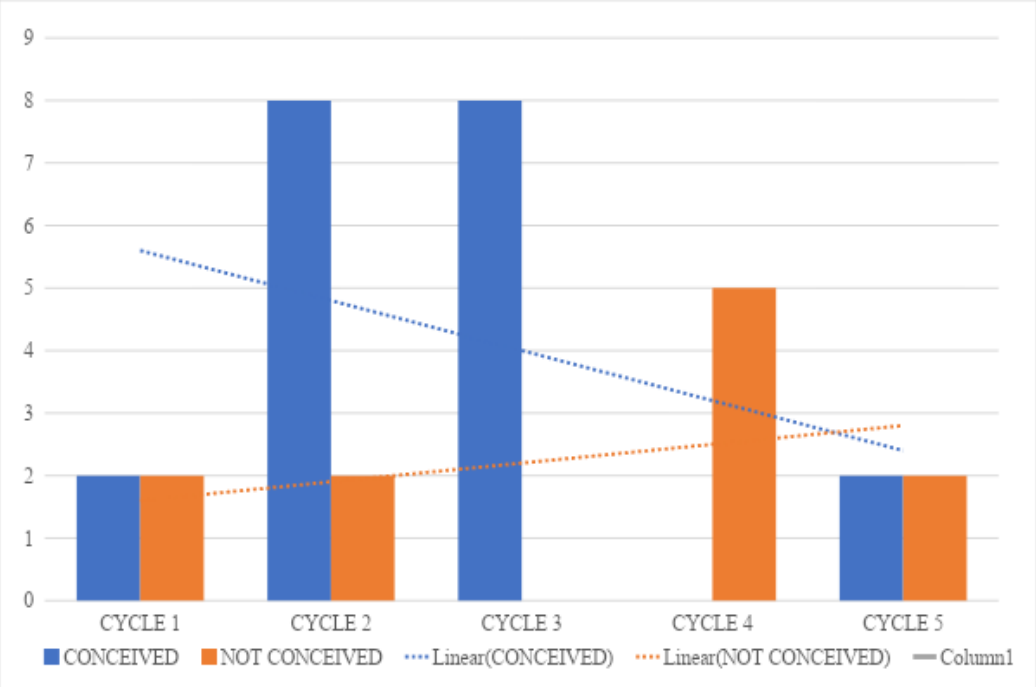


Table no5: Shows the number of patients conceived and not conceived during a five cycle therapy with Clomiphene Citrate.

DRUG	CYCLES	VARIABLES	NO. OF PATIENTS
CLOMIPHENE CITRATE	CYCLE 1	CONCEIVED	2
		NOT CONCEIVED	2
	CYCLE 2	CONCEIVED	8
		NOT CONCEIVED	2
	CYCLE 3	CONCEIVED	8
		NOT CONCEIVED	0
	CYCLE 4	CONCEIVED	0
		NOT CONCEIVED	5
	CYCLE 5	CONCEIVED	2
		NOT CONCEIVED	2



Statistical Analysis:

Table no6: Shows the follicular sizes of the patients during the days 11-17 of their menstrual cycle when treated with Clomiphene Citrate.

FOLLICULAR SIZE (CLOMIPHENE CITRATE)			
DAY 11	DAY13	DAY15	DAY17
11	14	18	23
5	5	6	6
9	14	18	23
11	15	19	25
10	14	18	21
11	15	19	22
12	16	20	24
11	14	19	24
10	15	19	23
11	14	18	22
5	5	6	6
11	14	18	22
9	14	20	24
8	9	9	9
12	17	19	24
6	6	6	6
9	10	11	11

6	8	8	8
10	10	10	10
10	14	19	22
10	17	24	26
10	14	19	24
11	15	20	25
9	9	9	9
10	15	19	24
11	15	19	24
11	16	20	24
8	8	8	8
10	14	18	24
9	9	9	9
11	15	20	25
9.580645	**12.58065**	**15.64516**	**18.36667**
1.8934	***3.53812***	***5.4194***	***7.4347***

Table no7: Shows the follicular sizes of the patients during the days 11-17 of their menstrual cycle when treated with Letrozole.

FOLLICULAR SIZE (LETROZOLE)			
DAY 11	DAY 13	DAY 15	DAY 17
9	13	19	24
12	13	18	22
10	13	17	21
14	18	20	24
18	21	23	22
12	15	19	22
10	15	20	22
12	15	20	24
11	16	20	24
11	16	20	26
11	15	20	24
9	14	18	20
10	13	19	23
8	12	18	24
4	4	5	8
10	13	19	23
11	16	19	25
10	14	18	23
10	15	19	24
11	18	19	22
10	14	19	24
12	19	20	23
11	14	19	23
11	16	20	24
11	15	18	23
9	9	9	9
10	14	18	23
10	15	20	24
8	8	9	9.5
7	7	8.5	9
6	9	9	9.5
10.25806	**13.83871**	**17.40323**	**20.90323**
2.40787	**3.52228**	**4.32901**	**5.4351**

Table no8: Shows the value of significance using ANOVA test

ANOVA table	**SS**	**DF**	**MS**	**F (DFn, DFd)**	**P value**
Treatment (between the columns)	105.4	3	35.13	F (3, 4) = 24.30	P=0.0050
Residual (within the columns)	5.783	4	1.446		
Total	111.2	7			

Table no9: Shows the Summary of ANOVA test for follicular size by multiple comparisons of the follicular size using Tukey – Kramer test

Tukey multiple comparison test	**Mean Diff.**	**95.00% CI of diff.**	**Significant?**	**Summary**	**Adjusted P Value**	
DAY11 vs. DAY13	-3.290	-8.185 to 1.605	No	ns	0.1589	A-B
DAY11 vs. DAY15	-6.605	-11.50 to -1.710	Yes	*	0.0182	A-C
DAY11 vs. DAY17	-9.716	-14.61 to -4.821	Yes	**	0.0044	A-D
DAY13 vs. DAY15	-3.315	-8.209 to 1.580	No	ns	0.1559	B-C
DAY13 vs. DAY17	-6.425	-11.32 to -1.530	Yes	*	0.0200	B-D
DAY15 vs. DAY17	-3.111	-8.006 to 1.784	No	ns	0.1829	C-D

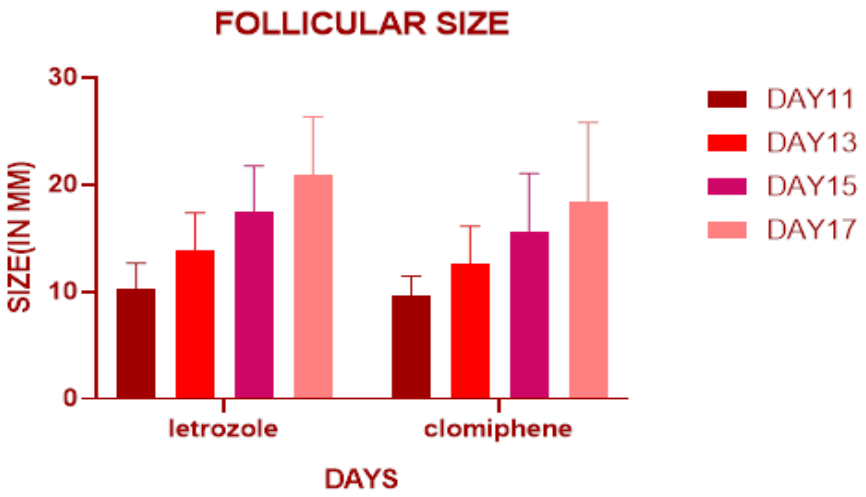


Figure depicts the Graphical representation of follicular size of letrozole and clomiphene citrate

Table no10: Shows the Endometrial Thickness of the patients during the days 11-17 of their menstrual cycle when treated with Letrozole.

ENDOMETRIAL THICKNESS (LETROZOLE)			
DAY11	DAY13	DAY15	DAY17
5	6	8	12
6	8	10	13
6	8	12	14
4	6	8	11
5	7	9	12
5	7	10	13
8	10	12	14
6	8	11	14
8	10	12	14
7	12	14	17
6	8	11	14
6	8	11	14
8	12	13	14
3	3	4	4
6	9	12	16
6	9	11	15
5	8	12	14
6	9	10	13
6	8	9	14
7	9	12	14
6	9	11	14
6	9	12	15
6	9	11	14
7	9	11	15
3	6	8	10
6	6	6	6
4	6	9	12

8	8.5	11	14
4	4	4	4
6	6	6	6
5	5	6.5	7
5.806452	**7.822581**	**10.20968**	**12.34615**
1.32714	***2.0271***	***2.86872***	***3.53205***

Table no11: Shows the Endometrial Thickness of the patients during the days 11-17 of their menstrual cycle when treated with Clomiphene Citrate.

ENDOMETRIAL THICKNESS (CLOMIPHENE CITRATE)			
DAY11	DAY13	DAY15	DAY 17
4	6	8	11
5	5	5	7
7	8	11	14
5	8	10	13
5	6	8	10
6	7	8	11
5	6	9	12
5	6	8	12
6	8	10	13
6	8	10	13
3	3	3	3
5	8	11	14
7	8	10	14
5	5	6	7
6	9	12	14
5	5	5	5
5.1	5.6	6	6
5	5	5	5
9	9.6	10	10
6	9	11	14
6	8	11	15
6	10	11	14
6	11	13	15
3	3	3	3
6	9	11	15
6	10	12	14
6	10	12	14
3	3	3	3
6	9	12	14
6	6	6.5	7
6	11	13	15
5.487097	**7.264516**	**8.887097**	**10.76667**
1.2063	***2.29166***	***3.14566***	***4.09948***

Table no12: Shows the Summary of ANOVA test for endometrial thickness.

ANOVA table	**SS**	**DF**	**MS**	**F (DFn, DFd)**	**P-value**
Treatment (between columns)	38.95	3	12.98	F (3, 4) = 22.30	P=0.0059
Residual (within columns)	2.329	4	0.5822		
Total	41.28	7			

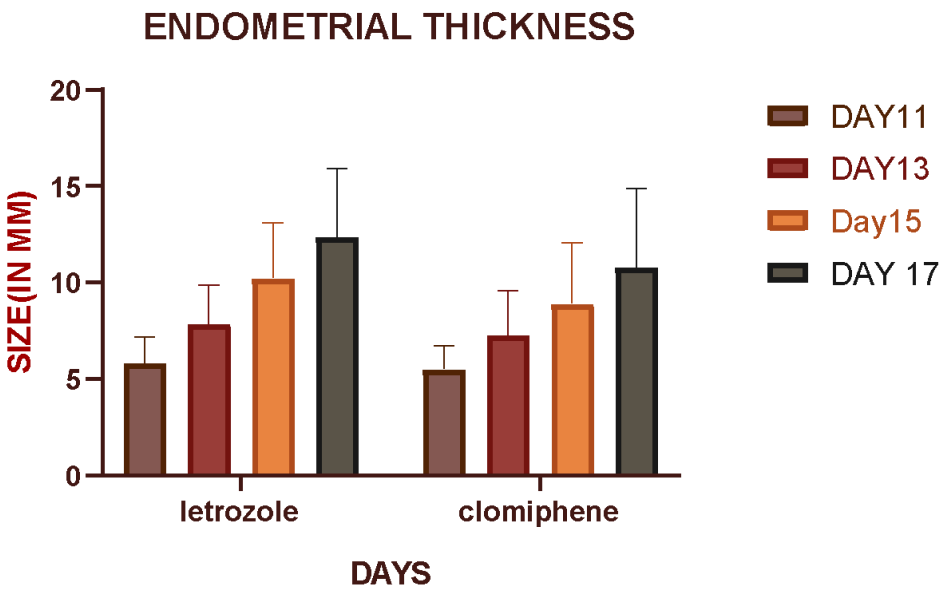


Figure depicts the Graphical representation of ANOVA for endometrial thickness.

IV. Discussion

Clomiphene citrate is the most prescribed medication for ovulation induction [18]. In compliance with the results of this study, the average endometrial thickness on day 17 was less when compared to that of the subjects taking clomiphene citrate to that of Letrozole. Patients with Letrozole obtained endometrial thickening due to better vascularization in comparison with clomiphene citrate. Clomiphene citrate has an anti-estrogenic effect and comparatively longer half-life that causes decreasing endometrial thickness by decreasing oestrogen receptors[13]. It was appropriate due to the triggering of ovulation and thickness of the endometrium that allows facilitating implantation of the fertilized ovum with Letrozole.

Some of the adverse effects of clomiphene and Letrozole on the outcome of infertility treatment due to the elevated hormone levels are explained. There is a low risk of insufficient uterine blood supply during the early luteal phase and the implantation period in clomiphene citrate outcomes.

Aromatase is the enzyme that catalyses the androsterone to oestrone and later to E2. Letrozole results in the blockage of oestrogen production both in the brain and peripheral tissues by a negative feedback mechanism, which ultimately leads to pituitary gonadotropin surge that stimulates ovarian follicular development[22].

The results of the study also assume that Letrozole is an acceptable alternative to clomiphene citrate in patients diagnosed with subfertility. A daily dose of 2.5mg/day shows ideal repression of serum oestrogen levels without any adverse effects. Therefore, 2.5mg/day for 5days is the admissible dose for any woman. Although, 2.5mg daily dose may fail to produce follicles in women, in those women 5- 7.5mg dose daily for 5 days is prescribed. The half-life of the drug is so low and eliminated quickly from the body leading to no accumulation. Thus, Letrozole is likely to produce mono follicular development, hence reducing the chances of multiple pregnancies.

V. Conclusion

This study shows the effectiveness of Letrozole in follicular diameter and endometrial growth in patients with subfertility compared to clomiphene. In addition, Letrozole is more effectively involved in ovulation than clomiphene. We, therefore, conclude that the triggering of ovulation by Letrozole is safe and effective.

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