

Comparison of effect of clomiphene citrate with estradiol valerate v/s letrozole on endometrial thickness in infertile women with PCOS

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Abstract

Background: Polycystic ovary syndrome is the commonest endocrinopathy in anovulatory infertility in young women. It is estimated that infertility affects 10 to 14% of the Indian population of which approximately 25-30% part occupied by PCOS.

Methods : This prospective study enrolled 180 infertile women with PCOS, age 21-35 yrs who have taken 1 cycle of clomiphene citrate 100 mg, endometrial thickness <7 mm in spite of follicles greater than 18 mm. Half of them treated with clomiphene citrate with estradiol valerate and remaining half with letrozole.

Results : In Group-A treated with clomiphene plus estradiol valerate mean endometrial thickness on day 3 was 5.5 mm, on day 10 was 6.2 mm, on day 12 was 6.8 mm, day 14 was 7.2 mm, day 16 was 7.6 mm, day 18 was 7.6 mm and on day of rupture endometrial thickness was 7.5 mm. In Group-B treated with letrozole mean endometrial thickness on day 3 was 5.3 mm, on day 10 was 6.8 mm, day 12 was 6.8 mm, day 14 was 7.4 mm, day 16 was 8.3 mm, day 18 was 8.3

mm and on day of rupture endometrial thickness was 8.5 mm.

Conclusion: Our study suggests that endometrial thickness was higher in group treated with letrozole.

Keywords: Polycystic ovary syndrome, Endometrial thickness

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy resulting in anovulatory infertility in young women. It is estimated that infertility affects 10 to 14% of the Indian population, of which approximately 25-30% part occupied by PCOS. PCOS understanding the main causes of infertility and selecting an appropriate treatment plan is a diagnostic and therapeutic priority.^{1,2}

Clomiphene citrate is the first line of treatment for ovulation induction in PCOS. The structure of Clomiphene is similar to estrogenic compounds and by blocking estrogen receptors reduces estrogen effect³.

Undoubtedly the endometrial thickness is one of the most important factors in infertility treatment. The pregnancy rate can be very low, especially if the

endometrial thickness is less than 6–8 mm⁴. However in a study by Sohrabvand et al, favourable changes were not observed from treatment with ethinyl estradiol⁵.

Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. Many researchers have studied this drug as an option for ovulation induction⁶. Letrozole induces agonistic effects of estrogen on endometrium rather than antagonistic effect. It induces ovulation by inhibiting the conversion of androgens to estrogen that creates an estrogen-deficient environment. Since this drug unlike Clomiphene does not block estrogen receptors and normal central feedback mechanisms remain intact, therefore, growing dominant follicle increases estrogen levels and by negative feedback decreases FSH, monofollicular growth occurs later⁷.

Methods

This hospital based prospective type of comparative study was conducted at Department of Obstetrics & Gynaecology, SMS Medical College, Jaipur during June 2018 to September 2019 after ethical clearance from study institutional review board and ethical committee, 160 infertile women diagnosed with PCOS who have taken 1 cycle of clomiphene citrate, endometrial thickness <7 mm in spite of follicles greater than 18 mm.

Inclusion Criteria

- Infertile women (age 21-35 years) with diagnosed PCOS who have taken 1 cycle of Clomiphene citrate 100 mg (endometrial thickness <7 mm in spite of follicles greater than 18 mm).
- Anatomical factors ruled out by diagnostic hysteroscopy and laparoscopy.

Exclusion Criteria

- Male factor infertility.
- Women with hyperprolactinemia, thyroid disorders, tubal blockage, uterine anatomical abnormalities.
- Women who are not giving written informed consent to participate in study.

Data collection was done as according to inclusion and exclusion criteria. After taking informed consent and reassuring regarding expertise and confidentiality, women were randomized into 2 groups: -

Group-A received 100 mg clomiphene citrate from day 3 to day 7 of menstrual cycle and 4 mg estradiol valerate the 8th day of menstruation until 14th day.

Group-B received 5 mg letrozole from day 3 to day 7 of menstrual cycle with placebo from 8th to 14th day of menstruation.

In both groups, follicular monitoring and endometrial thickness measurement was done by TVS when follicular size reached 18 mm. Triggered by inj. hCG 10,000 IU IM. Intrauterine insemination on rupture of follicle. Pregnancy diagnosed by beta hCG level and than by USG. The patients were followed for pregnancy rate.

Results

In this study Group-A mean endometrial thickness of day 3 was 5.5 mm, on day 10 was 6.2 mm, day 12 was 6.8 mm, day 14 was 7.2 mm, day 16 was 7.6 mm, day 18 was 7.6 mm and on day of rupture endometrial thickness was 7.5 mm.

Author founds endometrial thickness was significantly higher in the letrozole group ($p < 0.01$) (Table-1).

In Group-A, 18 patients (16.3%) conceived after treatment and in Group-B, 26 patients (32.5%) conceived.

Author founds pregnancy rate was significantly higher in the letrozole group ($p < 0.001$) (Table-2).

Table 1 : Distribution of Cases According to Endometrial Thickness

Endometrial Thickness	Day 3	Day 10	Day 12	Day 14	Day 16	Day 18	Day of Rupture
Group-A	5.5±0.5	6.2±0.5	6.8±0.5	7.1±0.5	7.6±0.5	7.6±0.5	7.5±0.5
Group-B	5.3±0.4	6.8±0.4	7.4±0.5	7.9±0.4	8.3±0.5	8.4±0.5	8.5±0.5
p-value	0.89	0.54	0.045	0.05	0.02	0.02	0.01

Table 2 : Distribution of Cases According to Outcome

Results	Group-A		Group-B		p-value
	No.	%	No.	%	
Conceive	13	16.25	26	32.50	0.001
Not	67	83.75	54	67.50	-
Total	80	100.00	80	100.00	

Discussion

PCOS is a common endocrine disorder in women of child-bearing age (6.8%), and is one of the most common causes of infertility due to ovulation disturbance.

The mean age of patients in our study was 25.8 ± 2.5 years in Group-A and in Group-B 26.3 ± 2.2 years. There were no significant difference between age in two groups. Seyedoshohadaei F et al (2016)⁸ found The mean age in Group-A and Group-B were 30.34 and 29.62 years ($p=0.381$). Rassol L et al (2019)⁹ found the mean age of Group-A was 31.2 and Group-B was 29.9 years ($p = 0.1025$).

We found that in Group-A 61.25% had 2 Dominant Follicles, 36.25% had 1 Dominant Follicles and 2.5% had 3 Dominant Follicles. In Group-B all patients had 1 Dominant Follicle. In Group-A On day 10 the mean

follicular diameter was 11.7 mm, on day 12 mean follicular diameter was 14.1 mm, on day 14 mean follicular diameter was 16.7 mm, on day 16 mean follicular diameter was 18.4 mm and on day 18 mean follicular diameter was 19.9 mm. In Group-B patients, On day 10 the mean follicular diameter was 11.7 mm, on day 12 mean follicular diameter was 14.1 mm, on day 14 mean follicular diameter was 16.4 mm, on day 16 mean follicular diameter was 18.0 mm and on day 18 mean follicular diameter was 18.6 mm. In study by Xi W et al (2015)¹⁰ use of Letrozole and Clomiphene citrate combined with gonadotropins in Clomiphene-resistant infertile women with PCOS was evaluated. The first group received the Letrozole + HMG, the second group received Clomiphene citrate + HMG, and the third group received HMG only. The rate of monofollicular development was 80.2% in the Letrozole + HMG group, 65.3% in the Clomiphene citrate + HMG group, and 54.7% in the HMG-only group. The difference between these three groups was significant statistically.

In our study In Group-A mean endometrial thickness on day 3 was 5.5 mm, on day 10 was 6.2 mm, day 12 was 6.8 mm, day 14 was 7.2 mm, day 16 was 7.6 mm, day 18 was 7.6 mm and on day of rupture endometrial thickness was 7.5 mm. In group-B mean endometrial thickness on day 3 was 5.3 mm, on day 10 was 6.8 mm, day 12 was 6.8 mm, day 14 was 7.4 mm, day 16 was 8.3 mm, day 18 was 8.3 mm and on day of rupture endometrial thickness was 8.5 mm. Seyedoshohadaei F et al (2016)⁸ showed that endometrial thickness was increased after administration of Clomiphene plus Estradiol Valerate and Letrozole, but there was significantly different in the two groups ($p<.05$). In

Letrozole group endometrial thickness was higher than Clomiphene plus Estradiol Valerate.

Endometrial thickness in the group receiving Letrozole was higher than other two groups¹⁰.

In a study by Satirapod C et al (2013)¹¹, the effects of Estradiol Valerate on the thickness of Clomiphene citrate -stimulated endometrium was examined. They concluded that the administration of Estradiol Valerate following the Clomiphene citrate treatment can prevent the endometrial thinning.

The results showed that the pregnancy rate in the Letrozole group was almost twice as Clomiphene plus Estradiol Valerate group and the difference was significant. We found that 13 patients (16.3%) in Group-A conceived after treatment and in Group-B 26 (32.5%) patients conceived.

This finding is also consistent with previous studies. Seyedshohadaei F et al (2016)⁸, evaluated the effectiveness of Clomiphene citrate, Tamoxifen and Letrozole in ovulation induction in infertile women. The pregnancy rate in Letrozole group was higher than Clomiphene citrate group, but the differences were not significant¹².

Conclusion

From study hospital based prospective comparative study, authors concluded that endometrial thickness was higher in group, treated with letrozole.

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