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Original Article

A prospective study for the assessment of follicular growth, endometrial thickness and serum estradiol levels in spontaneous and clomiphene citrate induced cycles in unexplained infertility patients

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ABSTRACT

Aim: Clomiphene citrate has an adverse effect on the normal cyclical growth of the endometrium by its antiestrogenic effect, thus making the endometrium thin and ineffective for subsequent implantation. **Objective:** 1. To evaluate follicular growth, endometrial thickness in spontaneous and clomiphene citrate induced cycle. 2. To estimate serum estradiol levels and correlate them with follicular growth and endometrial thickness in spontaneous and clomiphene citrate induced cycle. **Study Design:** This prospective study was conducted between Aug 2007 to Aug 2009 at the infertility clinic of department of OBG, Aarupadai Veedu Medical College, Pondicherry. This study was done to evaluate follicular growth, endometrial thickness and serum estradiol levels in spontaneous and clomiphene citrate induced cycles during preovulatory phase of menstrual cycle. Each woman was evaluated using transvaginal ultrasonography and serum estradiol level estimation from day ten of menstrual cycle until ovulation and result were analyzed using paired t-test. **Result:**

The groups were comparable with respect to wife age, husband's age; sperm count follicular growth, endometrial thickness, serum estradiol level. In spontaneous cycle growth of follicle was 2.8mm per day, endometrial thickness growth was 0.57 mm per day, both were found to be significant ($P < 0.0001$). Where as in study group growth of follicle was 2.87 mm per day and endometrial thickness growth was 0.47 mm per day the range of serum estradiol level was 45 to 2800 pg / ml in study group. In control group serum estradiol range was found to be 30-440 pg / ml from day 11 to day 14, Which was also statistically significant ($P < 0.0001$).

Conclusion: The leading follicular diameter was significantly larger in study group compared to control group, endometrial thickness was significantly diminished in study group in spite of increased estradiol levels.

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1. Introduction

Ovulation is the most crucial event in the human reproductive cycle and anovulatory disorders rank high among causes for female infertility. Clomiphene citrate competing with natural estrogen, occupies the estrogen receptor in the hypothalamus, diminishes the negative feed back, thus increasing the pulse amplitude of GnRH. This helps in release of gonadotropins, which acts on ovary to bring about ovulation. It also acts as an antiestrogen on target tissues like vagina, cervix and uterus. Thus effect of estrogen will be antagonized on above organs.

Fleisher et al [1] were the first to study the effect of clomiphene citrate on endometrium and they observed that the endometrial thickness was inversely proportional to clomiphene citrate dosage. Studies have also showed a delay in ovulation by an average of 3 days in majority [2,3] explanation may include blockade of estrogen related positive feed back or ovarian inhibitory factor. The purpose of this study was to found out the estrogenic, antiestrogenic effect of clomiphene citrate on endometrial thickness, ovulation, and serum estradiol in induced cycles and also to measure above parameters in spontaneous cycles.

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2. Material and Methods

This prospective study was conducted between Aug 2007 to Aug 2009 at the infertility clinic of Dept of OBG, Arupadai Veedu medical College, Pondicherry.

With this objective in view 60 infertility couples with unexplained infertility were recruited by the following criteria.

2.1. Inclusion Criteria

After doing investigation to rule out a possible causes of infertility they were studied in a spontaneous cycles followed by an induced cycle, by giving clomiphene citrate within the age group of 20-35. The spontaneous cycle served as control and induced cycle served as study group. In each cycle transvaginal ultrasonographic assessment of follicular growth and endometrial thickness were done. Serum estradiol level was measured from day 10 of menstrual cycle until ovulation.

2.2. Exclusion Criteria

1. Patients with other cause of infertility are excluded as.
2. Genital tuberculosis
3. Endometriosis
4. Tubal block
5. Uterine and Cervical anomalies
6. Other male infertility causes

2.3. Dosage Regimen And Medications

Clomiphene citrate 150mg of from day 5-9 of the menstrual cycle was given to evaluate the parameters for study group.

2.4. Evaluation

1. Age
2. Duration
3. Medical and Gynecology history
4. P/S and P/V to rule out adnexal pathology
5. Semen analysis
6. Estimation of Serum estradiol by RIA.
7. Transvaginal Sonography done for measuring follicular diameter and endometrial thickness in spontaneous and in clomiphene induced cycles.

3. RESULTS

Control groups and study group had 60 patients each. Both the groups were comparable with respect to the age of wife, age of husband, duration of infertility, sperm count of husband (Table 1).

TABLE 1 - DEMOGRAPHIC TABLE

	Mean \pm SD
Age of Wife	25.90 \pm 2.38
Age of Husband	25.97 \pm 2.38
Duration of infertility	5.05 \pm 2.27
Sperm count of husband	93.40 \pm 9.09

Table 2 shows the follicular diameter in study group and control group, which increased progressively from day - 4 to day - 1. Follicle increased by 2.8 mm per day in control group with

average size of 11.390mm, where as it increased by 2.87mm per day in study group, with average size of 11.425 mm which is statistically significant.

Mean follicular diameter in the immediate preovulating phase was 20.98 \pm 1.62 mm in control group and 23.02 \pm 1.58 in study group.

TABLE 2 - COMPARISON OF FOLLICULAR DIAMETER BETWEEN CONTROL AND STUDY GROUP

Day of Cycle	Mean follicular diameter \pm SD		P Value
	Control Group	Study Group	
Day 4	9.55 \pm 0.70	11.51 \pm 1.14	<0.0001
Day 3	12.33 \pm 1.57	14.44 \pm 1.23	<0.0001
Day 2	16.32 \pm 1.57	18.20 \pm 1.75	<0.0001
Day 1	20.98 \pm 1.62	23.02 \pm 1.58	<0.0001

Table 3 shows endometrial thickness which increased by 0.57mm per day in control group 0.47 mm in study group. The average increase was 3.2 mm and 2.48 mm in study group and control group, which was statistically significant. The range was between 4 -12.2 mm in control group and 4.6 - 7 mm in study group.

TABLE 3 - COMPARISON OF ENDOMETRIAL THICKNESS GROWTH BETWEEN CONTROL AND STUDY GROUP

Day of Cycle	Mean follicular diameter \pm SD		P Value
	Control Group	Study Group	
Day -4	7.42 \pm 1.72	6.94 \pm 1.21	0.040
Day -3	8.17 \pm 1.29	7.39 \pm 1.00	<0.0001
Day -2	9.15 \pm 1.22	8.54 \pm 1.09	0.004
Day -1	10.02 \pm 1.15	8.76 \pm 1.53	<0.0001
Day 0	10.89 \pm 1.06	9.37 \pm 1.17	<0.0001

Table 4 shows, Serum estradiol levels which increased from day 11-14 in both control and study groups. The range was 30 to 440 pg/ml in control group and 45 to 2800 pg / ml in study group, which was statistically significant. Higher estradiol levels obtained on each day from day 11-14 of induced cycle as compared to the control cycle.

TABLE 4 - COMPARISON OF SERUM ESTRADIOL LEVELS IN CONTROL AND STUDY GROUP

Day of Cycle	Mean follicular diameter \pm SD		P Value
	Control Group	Study Group	
11	84.98 \pm 32.30	233.28 \pm 222.92	0.0001
12	133.02 \pm 56.65	330.42 \pm 289.08	0.0001
13	182.95 \pm 55.17	568.60 \pm 489.67	0.0001
14	258.80 \pm 63.78	598.74 \pm 648.62	0.0001

4. Discussion

The results of this study confirmed that average increase of size of follicle was 11.390 in control group of 11.425 in study group. Follicular diameter in clomiphene citrate induced cycle was significantly large than in control group on all days of comparison. This effect of clomiphene citrate on follicular phase as been previously documented by Thorneycraft et al and Hecht et al [2,3] In the present study endometrial thickness increased progressively in both control as well as study group cycles, to reach a maximum two days prior to ovulation. This is in agreement with the previous studies [4,5,6,7,8].

Serum estradiol levels on all days of the Preovulatory phase was significantly high in the study group. The peak E2 level was 265 ± 68.56 pg/ml the control cycle as against 862.05 ± 668.87 pg/ml in the study cycle ($P=0.0005$) Table 5 shows the comparison of serum estradiol level in present study with other studies. [9,10,11].

TABLE 5 - COMPARISON OF SERUM ESTRADIOL LEVELS IN THE PRESENT STUDY WITH OTHER STUDIES

Author	Year	Serum E2 levels		Statistical Significance
		Control	Study	
1. Maxson et al	1984	337 ±18 pg/ml	1254±102 pg/ml	+
2. Tepper et al	1988	382 ±1.55 pg/ml	915 ±430 pg/ml	+
3. Asaad et al	1993	410 Pmol/ml	1358 pmol/ml	+
4. Present Study	2009	258.80 ±63.78	598.74 ±648.62	+

5. Conclusion

This study has shown that leading follicular diameter was significantly larger in the clomiphene citrate, when compared to the spontaneous cycles. Endometrial thickness was significantly decreased in the clomiphene citrate induced cycles inspite of increased serum estradiol levels, when compared to spontaneous cycles.

The present study demonstrates that the "clomiphene citrate adversely affect the growth of the endometrium which may contribute to the discrepancy in its ovulation and pregnancy rate".

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