

Comparative Evaluation of Follicular Development and Endometrial Thickness in Spontaneous and Clomiphene Citrate Induced Cycle in Unexplained Infertility

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ABSTRACT

Background: Unexplained infertility is one of the major causes of female infertility and ovulation induction is used as a standard treatment for such cases. Clomiphene citrate is commonly used drug for induction of ovulation.

Aims: To assess follicular growth, endometrial thickness and timing of ovulation in Spontaneous and Clomiphene Citrate Induced Cycle in Unexplained Infertility.

Material and Methods: This prospective study was conducted in Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India, after taking ethical clearance from institutional ethical committee. A total of thirty unexplained infertility cases were enrolled in the study. Each woman was evaluated by transvaginal ultrasound, first on day 3 of menstrual cycle for baseline assessment, then from day eight, every alternate day until ovulation. They were evaluated first in a spontaneous cycle followed by an induced cycle with clomiphene citrate 50 mg daily for 5 days from day 3 to 7 of cycle. SPSS software and paired t-test were used for analyzing the results. P value less than 0.05 was considered for statistical significance.

Results: The leading follicular diameter was significantly

larger, endometrial thickness was significantly diminished and ovulation occurred earlier in Clomiphene Citrate induced cycle when compared to spontaneous cycle.

Conclusion: Clomiphene citrate induced cycles showed different follicular growth, endometrial thickness and timing of ovulation compared to spontaneous cycles.

Key Words: Unexplained infertility, Clomiphene citrate, Follicular development, Endometrial thickness.

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INTRODUCTION

Anovulatory disorders and unexplained infertility are among major causes for female infertility and ovulation induction is used as a standard treatment for such patients. Ovulation induction involves stimulating the ovary to produce one or more eggs. The rationale for ovulation induction in women with unexplained infertility is to enhance the likelihood of pregnancy by increasing the number of oocytes available for fertilization. It may be accomplished with a number of different medications. Clomiphene citrate (CC) is most commonly prescribed medicine for induction of ovulation. It is also used in combination with IUI as an empiric treatment for unexplained infertility.

Clomiphene citrate is a racemic mixture of zuclomiphene (cis-isomer with mild oestrogenic and anti-oestrogenic activity) and endclomiphene (trans-isomers with only antioestrogenic activity). Endclomiphene is active form, which has short half-life. On the other hand zuclomiphene is inactive form and has longer half-life. It

is a weak estrogen; its predominant role is probably that of an antiestrogen. It competes with natural estrogen, occupies the estrogen receptor in the hypothalamus and diminishes the negative feedback, thus increasing the pulse amplitude of GnRH. This helps in release of gonadotropins, which acts on ovary to bring about ovulation. Activity of clomiphene may be influenced by En/Zu isomer ratio in the tablet and also in the individual circulation, individual metabolism, dosage regime and timing of administration in relation to menstruation cycle.

In women with unexplained infertility, follicular growth has been found to be enhanced in CC induced cycles by most of the studies¹⁻³. Its effect on endometrium is controversial. While Randall et al³ showed reduced endometrial thickness in CC cycle, Esmat Baroti⁴ showed no difference in CC and spontaneous cycle. Sereepapong W et al⁵ showed no reduction in endometrial thickness but associated with reduction in glandular density. Thus

endometrial thickness and its growth patterns may be a factor contributing to the discrepancy between ovulation and pregnancy rates with the use of CC. A study by Wolman I et al⁶ has shown that thicker endometrium with higher average growth rate was observed in the group that achieved pregnancy with clomiphene citrate compared to those who not achieved pregnancy with CC in unexplained infertility cases.

The purpose of this study was to find out the estrogenic and antiestrogenic effect of clomiphene citrate on follicular growth, endometrial thickness and timing of ovulation in induced cycles and also to measure above parameters in spontaneous cycles in unexplained infertility cases.

MATERIALS AND METHODS

This was a prospective study conducted between May 2013 to June 2014 in the department of Obstetrics & Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, after taking ethical clearance from institutional ethical committee. After thorough evaluation and history taking, a total of 30 infertile women who were diagnosed to have unexplained infertility, fulfilling the inclusion /exclusion criteria were enrolled in the study.

Each patients were evaluated by using transvaginal ultrasonography (sonalisa 32, machine no.Y09V4115 Delhi, India), first on day 3 for baseline assessment and then from day eight, every alternate days until ovulation. They were evaluated first in a spontaneous cycles followed by an induced cycle, by giving clomiphene citrate 50 mg daily for 5 days from day 3 to day 7 of cycle. In each cycle transvaginal ultrasonographic assessment of follicular growth and endometrial thickness were done.

Inclusion criteria

Infertile women aged between 20-35 years with unexplained infertility were enrolled in this study.

Exclusion criteria

- Patients with tubal or male factor infertility
- PCOD
- Endometriosis

- Genital tuberculosis
- Uterine and Cervical anomalies
- Infertility with endocrinal disorders

Evaluation

A complete infertility work up was done in all cases. This included a detailed clinical history, physical and pelvic examination and following infertility investigations:

- CBC with ESR
- Day 3 LH, FSH
- Husband’s semen analysis
- HIV, HBsAg, VDRL
- Thyroid function tests
- Prolactin level
- Blood sugar
- Monteux test and chest X ray
- Pelvic ultrasound to rule out any pre-existing ovarian cyst, to assess baseline ovarian morphology and to rule out any uterine abnormalities.
- Premenstrual endometrial biopsy for detection of ovulation and to rule out endometrial tuberculosis
- Hysterosalpingography to confirm patent fallopian tubes.

RESULTS

Group A: Spontaneous cycle; Group B: Induced cycle

Follicle size

Group A: (n=30) - Maximum follicle size attained was 25mm with the mean of 18.1 and standard deviation of 2.155

Group B: (n=30) Maximum follicle size attained was 25mm with a mean of 20.3 and a standard deviation of 2.950. Comparing both the groups, level of significance is .004 which is significant.

Preovulatory size of the follicle

Group A: Mean size of follicle when it ruptures in spontaneous cycle was 17.93 with the standard deviation of 2.196

Group B: mean size of follicle when it ruptures in induced cycle was 20.47 with the standard deviation of 2.980.

Comparing the two results level of significance is .001 which is significant.

Table 1: Comparison of largest Follicle size in mm

	15-18mm	19-22mm	23-26mm
Group A(n=30)	22 (73.26%)	7 (23.31%)	1 (3.33%)
Group B(n=30)	11 (36.63%)	11 (36.63%)	8 (26.64%)

Table 2: Comparison of follicular size, day of ovulation and endometrial thickness between spontaneous and CC induced cycle

	Largest Follicle Size (mm)		Preovulatory size of follicle (mm)		Day of ovulation		Endometrial thickness at ovulation (mm)	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
N	30	30	30	30	30	30	30	30
Minimum	15	16	15	16	14	12	7.1	6.5
Maximum	25	25	25	25	19	18	10.5	9.8
Mean	18.10	20.30	17.93	20.47	15.70	13.73	8.537	8.103
Standard Deviation	2.155	2.950	2.196	2.980	1.557	1.639	.9463	.6790
Median	18.00	20.00	18.00	20.00	16.00	14.00	8.200	8.150
P value	0.004		0.001		0.000		0.026	

Table 3: Comparison of preovulatory follicle size

	15-16mm	17-18mm	19-20mm	21-22mm	23-25mm
Group A(n=30)	9 (29.97%)	14 (46.62%)	4 (13.32%)	2 (6.66%)	1 (3.33%)
Group B(n=30)	3 (9.99%)	8 (26.64%)	8 (26.64%)	2 (6.66%)	9 (29.97%)

Day of the ovulation

Group A: Mean day of cycle when it ruptures was 15.7 with the standard deviation of 1.557

Group B: Mean day of cycle when it ruptures was 13.73 with the standard deviation of 1.639

Comparing both the cycle level of significance is .000 which is highly significant.

Endometrial thickness at ovulation

Group A: mean endometrial thickness at ovulation is 8.537 with the standard deviation of .9463

Group B: mean endometrial thickness at ovulation is 8.103 with the standard deviation of .6790

Comparing the two cycles the level of significance is .026 which is significant.

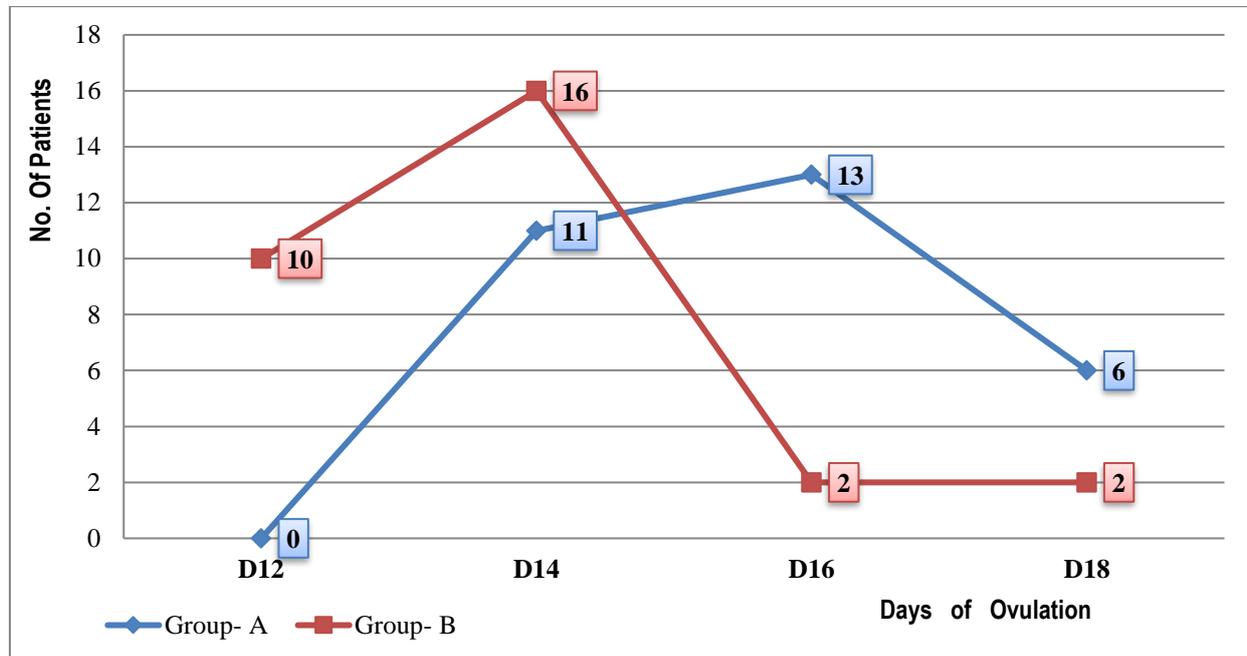


Figure 1: Comparison of Day of Ovulation

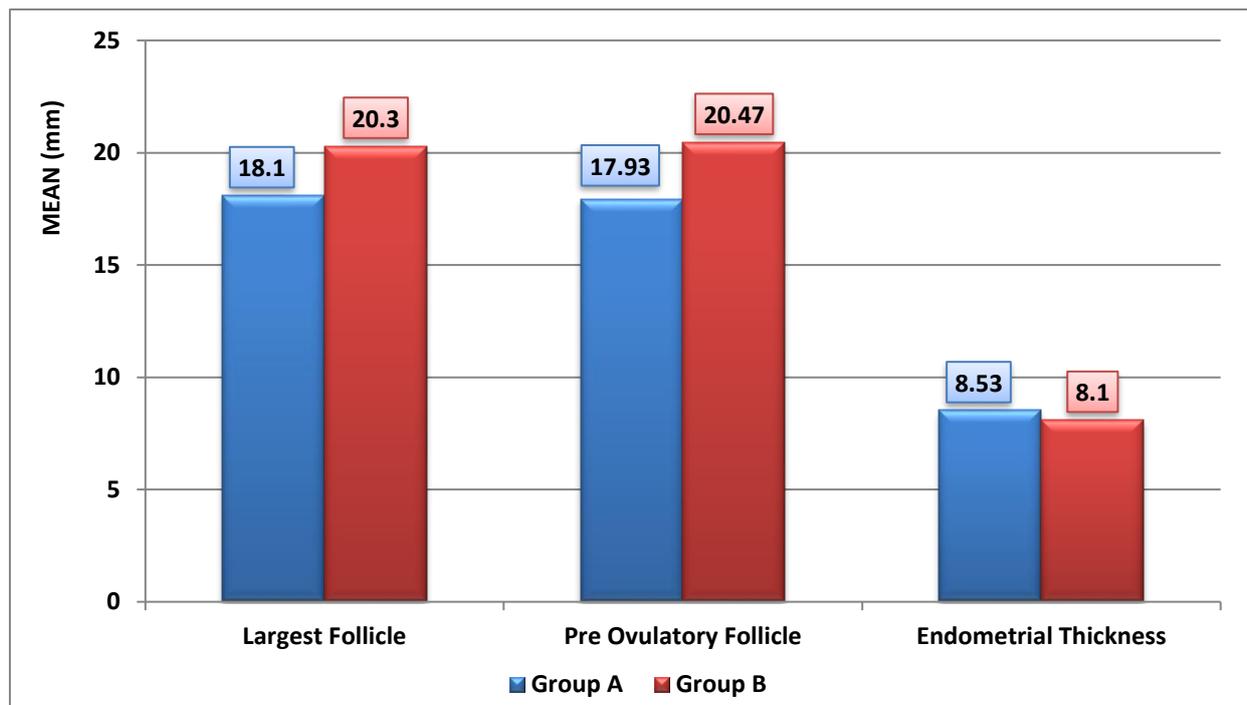


Figure 2: Comparison of Mean Value of Largest Follicle Size, Pre-ovulatory Size of Follicle & Endometrial Thickness in both groups

DISCUSSION

In the present study mean age of infertile women was 27+/- 3 years with range of 20-35 years; mean duration of infertility was 5.23 years with range of 2-15 years. Mean FSH on day 3 of cycle was 6.48 mIU/ml +/- 2.17 and mean LH was 5.60 mIU/ml +/- 3.02. All spontaneous and CC induced cycle were ovulatory.

In this study largest follicle size attained was 25 mm in both group with mean 18.10 mm in group A and 20.30 in group B. This shows follicular diameter in clomiphene citrate induced cycle was significantly larger than spontaneous cycle. This observation was found to be in agreement with previous studies¹⁻³. Study by Esnot

Baraoti (2008)⁴ showed that CC induced cycle had no different follicular growth in comparison to spontaneous cycle.

Mean size of the follicle when it ruptures was 17.93 with SD 2.19 in spontaneous cycle and 20.47 with SD 2.98 in induced cycle. This shows that mean follicular size in the immediate preovulatory phase was 2-3 mm larger in induced cycle. This is in agreement with study done by Sangeeta Meenakshi et al⁷.

In the present study ovulation occurs earlier in CC induced cycle. The mean day of ovulation was 15.7 in group A, with 80 % cases had ovulation between D14-16 while in group B it was 13.73 with 86.6% had ovulation between D12-14. This is in disagreement with study done by Huneus A et al² which showed delayed ovulation in CC cycle with 16.1 in CC cycle and 15.1 in spontaneous cycle.

Mean endometrial thickness at ovulation in group A was 8.537 with the standard deviation of 0.94 and mean endometrial thickness at ovulation in group B was 8.103 with the standard deviation of 0.67. The difference is statistically significant. This shows CC decreases endometrial thickness. This is in agreement with previous studies^{1-3,7}. However studies by Esmat Baroti (2008)⁴ and Sereepong (2000)⁵ show no effect on endometrial thickness. Dehabashi S et al (2003)⁸ had reported significantly diminished thickness in late proliferative phase but no significant difference in midsecretory phase.

Many studies have correlated pregnancy rates with endometrial thickness⁹⁻¹¹. They have reported that no pregnancy occurred when endometrial thickness was 6 mm or less, and that the chance of pregnancy was greatest with endometrial thickness 9-10 mm or more. Dickey R P et al⁹ also shown that continuing pregnancy rate was higher when endometrial thickness was > or = 9 mm compared to when it was 6 to 8 mm in thickness.

CONCLUSION

This study has shown that leading follicular diameter was significantly larger and ovulation occurs earlier in the CC induced cycle when compared to spontaneous cycle. Endometrial thickness was significantly decreased in induced cycle which may contribute to discrepancy in its ovulation and pregnancy rate.

CLINICAL SIGNIFICANCE

With the currently ban of Letrozole drug in India (since 2011) for ovulation induction, clomiphene citrate remain most commonly used drug for this purpose especially in unexplained infertility cases. Although the current racemic mixture of clomiphene citrate seems to be safe, controversy exists of its effects over endometrium which is of great concern in achieving pregnancy rate. Monitoring its effect on various parameters in individual cycle will help in better control of cycle to achieve higher pregnancy rates.

ETHICAL APPROVAL

Approved by institutional ethical committee.

REFERENCES

1. Hariitha S, Rajagopalan G. Follicular growth, endometrial thickness, and Serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. *Int J Gynaecol Obstet* 2003; 81:287-92.

2. Huneus A, Hess R, Triantafilo Y, Parada M, Alam V. Follicular and Endometrial growth profiles in stimulated cycles with clomiphene citrate. *Rev Chil Obstet Gynecol* 1994; 59:463-8.

3. Randall JM, Templeton A. Transvaginal sonographic assessment of follicular and endometrial growth in spontaneous and clomiphene citrate cycles. *Fertil Steril* 1991;56(2):208-12.

4. Esmat Baroti, Elham Nelsan samani. Transvaginal Sonographic Assessment of the Follicular Development and Endometrial Thickness in Spontaneous and Clomiphene Citrate-Induced Cycles. *Journal of family & Reproductive health* 2008; vol 2 no 1:49-51.

5. Sereepapong W, Suwajanakorn S, Triratanachat S, Sampatanukul P, Pruksananonda K, Boonkasemsanti W, et al. Effects of clomiphene citrate on the endometrium of regularly cycling women. *Fertil Steril* 2000; 73:287-91.

6. Wolman I, Sagi J, Pauzner D, Yovel I, Seidman DS, David MP. Transabdominal ultrasonographic evaluation of endometrial thickness in Clomiphene citrate-stimulated cycles in relation to conception. *J Clin Ultrasound* 1994; 22:109-12.

7. Sangeetha Meenakshi. R, Shobha.U.N, Thavamani Devi .T, 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. *Int J Biol Med Res.* 2012; 3(1): 1345-1347

8. Dehbashi S, Parsanezhad ME, Alborzi S, Zarei A. Effect of clomiphene citrate on endometrium thickness and echogenic patterns. *Int J Gynaecol Obstet.* 2003; 80 (1): 49-53.

9. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. *FertilSteril*1993;59:756-60.

10. Isaacs JD Jr, Wells CS, Williams DB, Odem RR, Gast MJ, Strickler RC. Endometrial thickness is a valid monitoring parameter in cycles of ovulation induction with menotropins alone. *Fertil Steril* 1996; 65:262-6.

11. Randall J M, Templeton A. The effects of clomiphene citrate upon ovulation and endocrinology when administered to patients with unexplained infertility. *Hum Reprod* 1991; 6:659-64.

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