

THE EFFECT OF CLOMIPHENE ON FOLLICULAR DYNAMICS AND ENDOMETRIAL THICKNESS

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SUMMARY

A study of 25 female partners of couples with unexplained infertility was conducted in Obstetrics and Gynaecology Department of M.A.M.C. and Associated L.N. Hospital to evaluate the effect of clomiphene citrate on follicular dynamics and endometrial thickness. All patients underwent transvaginal sonography over two consecutive cycles - spontaneous followed by clomiphene induced cycle. It was found that mean leading follicular diameter was larger in clomiphene induced cycle at all points studied. The dimensions on one day prior to ovulation was 2.598 cm in induced cycles and 2.10 cm in spontaneous cycle ($P < 0.01$). Endometrial thickness, however, was reduced at all points studied in the induced cycle and dimension was 0.92 cm in induced cycle and 1.008 cm in spontaneous cycle ($P < 0.01$) on day of ovulation.

INTRODUCTION

Ovulation is a major and crucial event in reproductive cycle. It has been conventionally studied by a rise in BBT,

endometrial histopathology, serum estradiol and LH surge. However with the advent of transvaginal sonography, a simple and non-invasive, more accurate method to study ovulation has been established. Ovulatory dysfunction contribute to about 40% of female

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infertility. Wide range of ovulation induction agents have been developed of which clomiphene has been the most commonly used drug for this purpose. However pregnancy rates with clomiphene are considerably lower than ovulatory rates. The ovulation success rates range between 57-91% (Gysler et al, 1982) and pregnancy rates are only 12-40%.

The mechanism most commonly proposed is the potential antiestrogenic effect of the drug on cervical mucus and endometrial thickness. The former can be now overcome by IntraUterine Insemination.

Different patterns of endometrial responses have been described but precise relationship between endometrial thickness and clomiphene has not been clarified. The effect of Clomiphene on follicular dynamics also remains controversial with some studies reporting larger diameter and others reporting no difference when compared with spontaneous cycles.

This study therefore was undertaken to evaluate the effect of clomiphene on follicular dynamics and endometrial thickness in cases of unexplained infertility.

MATERIAL AND METHODS

The study comprised of 25 female partners of infertile couples with unexplained infertility. All cases were attending the Obstetrics and Gynaecology outpatient Department of MAMC and Associated Lok Nayak Hospital, New Delhi.

Each patient was subjected to a

thorough history taking, general physical examination, systemic examination and pelvic examination and after relevant investigation the selection criteria was fulfilled if 1) Age of patient was 20-35 years 2) Normal pelvic examination 3) Ovulatory cycles 4) No systemic or endocrinological disease 5) Normal husband semen analysis 6) Normal postcoital test 7) Patent tubes.

Each subject was studied over two consecutive cycles a) Spontaneous ovulatory cycle followed by b) Clomiphene induced cycle (Dosage 100 mg per day for day 5 to 9 of menstrual cycle. Transvaginal sonography was performed on Philips Ultrasound Systems (SDR Philips 1550 xp) using 5 MHz endovaginal probe.

The patient was briefly explained the procedure and reason for the transvaginal sonography. Immediately before each examination patients were instructed to empty their bladders. The scan was performed with the patient in the dorsolithotomy position. The probe was introduced into the vagina gently and manipulated around the cervical lips to depict the structures of interest in best details. The endometrial thickness was measured by aligning the uterus along the central longitudinal axis avoiding the tangential view. It was measured from the echogenic interface of the junction of endometrium and myometrium avoiding the hypoechogenic halo. The halo represents the inner layer of compact and vascular myometrium. The presence of anechoic follicles within the ovary generally makes identification easy. Usually ovaries are

imaged between uterus and internal iliac vessel. Maximum follicular diameters were determined in three planes perpendicular to each other and a mean follicular diameter was calculated. The number of developing follicles was also noted.

Transvaginal sonological assessment was carried out on each patient starting on day 10 of the menstrual cycle and repeated on alternate days till follicular diameter reached a size of 16mm. Then daily assessment was done till ovulation occurred. Repeat examination was done on 7 days after evidence of ovulation to see endometrial thickness. On each examination sonological assessment of follicular and endometrial growth was done.

The diagnosis of ovulation was made by decrease in size or collapse of the mature follicles with the development of internal echoes and by presence of fluid in cul-de-sac. The day of the ovulation was labeled as day O so that the day before ovulation was day -1 and so on. Comparison between the spontaneous and clomiphene cycles was done on day -3, day -2, day -1, day O and day +7.

The results were analysed by using paired " T " Test.

RESULTS AND OBSERVATIONS

The mean age of the patients in our study was 26 years ranging between 22-34 years of age.

The average total length of the menstrual cycle was longer in clomiphene induced cycle (29.24 +/- 1.589 days) as compared to the spontaneous cycle

(27.84 +/- 2.304 days) ($P < 0.01$). This increase was entirely due to an increase in proliferative phase in clomiphene induced cycle (15.24 +/- 1.589 days) as compared to spontaneous (14.84 +/- 2.304 days)

All spontaneous cycles were monofollicular and ovulatory. However in clomiphene cycle the mean number of follicles greater than 16 mm was 2.58 +/- 1. Four cycles showed monofollicular and rest 21 cycles showed multifollicular development. All cycles were ovulatory with rupture of at least one follicle.

Leading follicular diameter increased progressively over the days of comparison reaching a maximum on day -1 in both spontaneous and clomiphene induced cycles (Table I).

The mean leading follicular diameter was significantly larger in clomiphene induced cycles as compared to spontaneous cycles on all the days of comparison reaching maximum on day -1 (Table I & $P < 0.01$). The mean dimensions on one day prior to ovulation were 2.10 +/- 0.339 cm (ranging from 1.6 cm to 3.0 cm) in spontaneous cycles and 2.628 +/- 0.409 cm (ranging from 1.9 to 3.3 cm) in clomiphene induced cycles.

The maximum leading follicular diameter showed a linear pattern of growth in both spontaneous and clomiphene induced cycles (Table I). The mean day to day growth rate was faster in clomiphene induced cycles (0.224 cm per day) as compared to spontaneous cycles (0.217 cm per day). However this increased rate of day to

TABLE I
COMPARISON OF EACH VARIABLE BETWEEN SPONTANEOUS AND
CLOMIPHENE INDUCED CYCLES

TABLE I
COMPARISON OF LEADING FOLLICULAR DIAMETER

Day	Mean Follicular Diameter		T Value	P Value
	Spont.	Clomi.		
(A) Day -3	1.676	2.150	6.28	< 0.01
Day -2	1.904	2.400	7.23	< 0.01
Day-1	2.104	2.598	7.65	< 0.01
(B) Gr. Rate	0.217cm/day	0.224cm/day	0.85	N.S.
(C) No. Of Folli. > 16mm	1	2.560 +/-1	-	-

TABLE II
COMPARISON OF ENDOMETRIAL THICKNESS

Day	Mean Endometrial Thickness		T Value	P Value
	Spont.	Clomi.		
Day -3	0.780	0.712	2.80	< 0.01
Day -2	0.840	0.776	2.70	< 0.05
Day -1	0.924	0.832	3.57	< 0.01
Day 0	1.008	0.920	3.16	< 0.01
Day +7	1.176	1.084	3.13	< 0.01
Gr. Rate	0.076cm/day	0.069cm/day	0.74	

day growth was not statistically significant. Thus leading follicular diameter in clomiphene induced cycle was significantly larger as compared

to spontaneous cycle but day to day growth rate was same in both.

Endometrial thickness in spontaneous cycles increased from a mean of

0.78 +/- 0.126 cm to 1.01 +/- 0.141 cm from three days prior to ovulation to the day of ovulation ($P < 0.01$). This phase showed a linear growth with average growth rate of 0.076 cm per day (Table II). The endometrial thickness increased to only 1.17 +/- 0.116 cm in 7 days after ovulation showing a plateau phase of growth.

In clomiphene induced cycles the endometrium showed a steady increase from 0.712 +/- 0.13 cm to 0.920 +/- 0.135 cm from three days prior to ovulation to the day of ovulation ($P < 0.01$). This phase showed a linear growth with an average growth rate of 0.069 cm per day (Table II). Again the increase in 7 days after ovulation was insignificant increasing from 0.920 +/- 0.135 cm on day of ovulation to 1.08 +/- 0.118 cm on seventh day after ovulation, showing a plateau phase of growth.

The endometrial thickness in clomiphene induced cycles when compared with spontaneous cycles was reduced at all points of comparison ($P < 0.01$). Although difference in growth rate per day was not statistically significant.

DISCUSSION

The mean length of the proliferative phase was longer in clomiphene induced cycles than spontaneous cycles. This finding is in agreement with results obtained by Fossum et al, 1990. The possible explanation for this was given by Messinis et al 1990. This was attributed to blockade of estradiol related positive feedback for LH surge

or ovarian inhibitory factors. This led to either delay of LH peak by delayed ovarian signal or delayed pituitary response to ovarian signal.

The total length of menstrual cycle was longer in induced cycles which was entirely due to increase in proliferative phase. All spontaneous cycles in our study were ovulatory with collapse and formation of corpus luteum. All spontaneous cycles, were monofollicular. In the clomiphene induced cycles in present study multifollicular development occurred with rupture of at least one preovulatory follicle. These observations are consistent with studies undertaken by Randall in 1991.

Leading follicular diameter was significantly larger in clomiphene induced cycles as compared to the spontaneous cycles at all points studied consistent with the previous studies reported by Randall et al 1991. Eden et al 1989 however found no difference in follicular diameter between spontaneous and clomiphene induced cycles. This could be explained because of lower dosage and earlier administration of clomiphene citrate in this study. The mechanism of increased leading follicular diameter in our study may be the prolongation of the follicular extended growth period.

Almost all studies show a linear pattern of growth of follicles as shown in present study. Though mean growth rate was higher in induced cycle the difference was not statistically significant. Eden 1980 and Randall

et al 1991 did not show any significant change in growth rate either.

Endometrial thickness increased progressively during the follicular phase of spontaneous and clomiphene induced ovulatory cycles as reported by Bakos et al 1994. The endometrial thickness plateaued during the luteal phase. These observations were confirmed in the present study. Eden et al, 1989, Bakos et al 1994 found a decrease in endometrial thickness at all points studied in clomiphene induced cycles. We found a decrease in endometrial thickness at all points studied (Table II). The possible explanation for this observation could be either histologic and ultrastructural abnormalities of endometrium due to antiestrogenic effect of clomiphene citrate or endometrial estrogen receptor depletion by clomiphene citrate, or both (Ronnberg et al, 1985; Gonen et al, 1989).

Therefore in our study we found

that the mean follicular diameter was larger in clomiphene induced cycle but the endometrial thickness was reduced at all points of comparison in clomiphene induced cycles thus confirming the antiestrogenic effect of clomiphene citrate on endometrium. This could be possible cause for discrepancy between pregnancy rates and ovulation rates achieved by clomiphene.

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