CLOMIPHENE CITRATE IN INFERTILITY AND ANOVULATION

by

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Introduction

Ovulation is the result of an integrated action between the hypothalamus, pituitary and ovaries. A well-balanced interaction between hypothalamic releasing factors, gonadotropic hormones, and ovarian steroids leads to an orderly ovulatory sequence. The gonadotropin releasing hormones stimulate the synthesis and secretion of FSH and LH which result in follicular maturation. During the process of follicular maturation, estrogen and other steroids are produced which in turn act on specific hypothalamic and pituitary receptors and induce an LH and FSH surge responsible for ovulation.

Failure to ovulate may be the result of dysfunction at any level of this complex system including higher brain centres, the hypothalamo-hypophyseal-ovarian axis and the steroid feedback system. By the same token ovulation can be induced or regulated by substances or factors produced at various levels.

The fact, that gonadal steroids or their analogues can and do control the release of the releasing factors (Schally *et al* 1975) for ovulation induction, has been used by various investigators for achieving this objective.

Clomiphene Citrate, an analogue of a synthetic non-steroid compound containing anti-estrogen and estrogen isomers was accidentally used for induction of ovulation by Greenblatt in the sixties (Greenblatt *et al* 1961). Since then there have been numerous reports on the ovulation inducing potential of this compound in patients with defective release of gonadotropins.

This presentation describes the results and changes in the various parameters used for monitoring this therapeutic regime.

Material and Methods

Clomiphene Citrate was given to 197 infertile women for a total of 513 cycles. These subjects were in the reproductive age group and had a complete sterility endocrine work-up. There was no tubal or pelvic pathology and the male factor was evaluated. The urinary gonadotropins, 17-ketosteroids and 17-ketogenic steroids were within normal limits. Thyroid function tests where indicated were also normal.

The patients presented themseves with a variety of menstrual patterns in addition to infertility of 3-15 years duration.

A number of clinical and laboratory parameters were used for monitoring the effects of this regime on ovarian activity (Table I). Daily plasma FSH, LH and

TABLE I

Parameters Used for Monitoring Ovarian Activ

1. Basal body temperature
2. Vaginal hormone cytology
3. Cervical mucus
4. Endometrial biopsy
5. Daily urinary estrone assays
6. Urinary pregnanediol assays
7. Plasma FSH and LH (Radioimmuno assays)

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urinary estrone (Brown) levels were estimated only in a limited number of patient-cycles.

The dosage varied from 50 mg daily to 200 mg daily for 4-5 days not exceeding a total of 600 mg per cycle. The patients maintained daily basal body temperature charts (BBT) and were closely monitored during the periovulatory period, i.e. immediately after completion of the therapeutic regime, by daily hormone assays, vaginal smears and cervical mucus changes. Urinary pregnanediol estimation or endometrial biopsy was carried out in the luteal phase.

Results

The overall incidence of ovulatory cycles in our group was 81.29%, whereas the conception rate was comparatively lower, 27.4% (Raphael, 1975) Table II.

The incidence of ovulation varied in the different clinical groups based on the menstrual patterns or presenting symptoms. It seemed that patients with regular menstrual cycles, and this included the habitual aborters had the highest incidence of ovulatory cycles, about 92% and also the highest conception rate, 29 pregnancies in 73 subjects i.e. 39.7% (Table III).

The incidence of ovulation and pregnancy in the group with irregular periods was comparable to the overall results with this regime. Cases of primary amenorrhea, though few, did not respond at all to this regime, whereas those who had developed amenorrhea later, showed an ovulatory incidence of 50%, but a very low pregnancy rate; only 3 pregnancies in 31 patients.

Patient assessment by initial cytohormonal tests or vaginal smears for evaluation of endogenous ovarian activity seemed to indicate that best results with clomid therapy were possible in cases where there was only a slight dysfunction in the pituitary-ovarian axis (Table IV).

TABLE II

Incidence of Ovulsion with Clomid

No. of Patients	No. of Cycles	No. of Ovulatory Cycles		Conception	
		No.	%	F T N D	Abortion
197	513	417	81.29%	39	15

TABLE III

Incidence of Ovulation Based on Menstrual Patterns

	Nos.	No. of Cycles	Ovulatory Cycles		No. of Pregnancies
			Nos.	%	
Regular Periods	68	200	185	92.50	26
Irregular Periods	87	228	188	82.5	22
Primary Amenorrhoea	6	9	X	X	X
Secondary Amenorrhoea	31	62	31	50	3
Habitual Abortion	5	14	13	92.9	3
Total:	197	513	417	81.3	54 (27.4%)

TABLE IV

Use of Initial Vaginal Smears in the Selection of Patients for Clomid Therapy

Smear Patterns	No. of Patients	Results with Clomid Therapy		
		No. of Cycles	Ovulatory	Pregnancy
L.E.I.	35	75	52.8%	2
M.E.I. with Fluctuation	33	108	76.0%	5
H.E.I.	19	52	69.4%	4
Luteal Phase Defects	50	139	90.3%	14

L.E.I. = Low Estrogenic Index M.E.I. = Moderate Estrogenic Index

H.E.I. = High Estrogenic Index

Cases of luteal phase defects responded with 90.3% ovulatory cycles and 14 pregnancies in comparison to those with low endogenous estrogen levels where the ovulation rate was 52.8% with only 2 pregnancies.

The therapeutic regime or dosage appeared to influence the ovulatory rate as shown in Table V, but was not statistically significant. Various dosage schedules were tried and it appeared that 50 mg for 5 days gave better results, 89.5% in comparison to other regimes.

It was important to assess the day of ovulation, especially in relation to dosage schedules.

It was noted that with 50 mg $\times$ 5 days regime, the maximum incidence of ovulation, 56.67% occurred on day 5-day 7 after the last tablet or D_{14}-D_{17} of a menstrual cycle. With higher dosage the day of ovulation seemed to occur at a little later stage (shift to the right) Table V.

In order to evaluate the effects of this drug on ovarian activity and ascertain the day of ovulation as closely as possible, changes in estrogen sensitive target tissues like vaginal epithelium (KPI) and cervical mucus (spinnbarkeit and Fern reaction) were correlated to urinary estrone patterns and basal body temperature dip.

Table VI demonstrates that in 99 out of 139 cycles, the vaginal smears showed anti-estrogenic patterns and cytolytic smears in the preovulatory period, whereas the cervical mucus reflected estrogenic activity by a highly positive Fern test, in a high percentage of these cases.

The urinary estrone, though done in a limited number of patient cycles in that group seemed to indicate a peak estrogenic effect just around ovulation time in all cases except one.

Table VII shows the timing of the peak values of the various ovulatory parameters in relation to post-Clomid period in a limited number of cycles (45) where daily urinary estrone assays were done and all patients were treated with 50 mg daily dose schedule. Plasma FSH and LH

TABLE V

Incidence of Ovulation Related to Dosage

Dosage	Total Treated Cycles	Ovulatory Cycles		Ovulatory Day			
		No.	%	PCD_1-D_4	PCD_5-D_7	$>PCD_7$	Date Unknown
50 mg for 5 days	134	120	89.55%	21.67%	56.67%	11.66%	10%
50 mg for 10-12 days	56	31	55%	16%	26%	10%	48%
100 mg for 4-5 days	166	138	83.1%	23.2%	28.2%	34.8%	13.8%
150 mg for 3-4 days	74	59	76%	23%	23%	45%	9%
200 mg for 2-3 days	83	69	81%	17%	30%	48%	5%
Total	513	417	81.3%				

TABLE VI

Correlation of Post Clomid Vaginal Smear Patterns to Other Parameters

Smear Patterns	Nos.	Cervical Mucus (Fern Test)		Estrone Curve	
		—Ve to +	++ To + ++	Flat	Rising
Antiestrogenic	99	21	78	3%	97%
Estrogenic	40	5	35	100%	

TABLE VII

Table Showing the Occurrance of B.B.T. DIP, Estrone Peak, Maximum Cervical Mucus Response, K.P.I. Peak, FSH Peak, LH Peak in the Post Clomid Period

Ovulatory Parameters	PCD_3-D_4	PCD_5-D_6	$>PCD_6$
B.B.T. DIP	18.3 %	50 %	31.7 %
Estrone Peak	29.8 %	54.2 %	16 %
Max. Cervical Mucus	27 %	49 %	24 %
K.P.I. Peak	27 %	50 %	23 %
F.S.H. Peak	25 %	63 %	12 %
L.H. Peak	13 %	87 %	—

were done only in 9 cycles. The ovulation day as indicated by these parameters seemed to occur most frequently (over 50% cycles) on PCD_5-PCD_6.

Table VIII shows the mean interval between LH peak and the onset of menstruation. The interval appears higher than what one encounters in normal cases. It is possible that there is increased luteal activity following clomid or it is also likely that some of these cases may be cases of early abortions.

TABLE VIII

Mean Interval between Midcyclic LH Peak and the Onset of Menstruation

Range	13—24 Days
Mean ± S.D.	18 ± 3.65

Discussion

The results of this study clearly demonstrate the scope of clomiphene therapy and its limitations in the treatment of infertility.

Cases of anovulation, luteal function defects and oligoovulators where there was adequate endogenous estrogen activity and a responsive endometrium, appeared most likely to benefit from this therapy.

Clinically best results were obtained in cases where menstrual patterns were regular even though the cycles may be anovulatory in comparison to those with irregular periods and cases of amenorrhea (Spellacy and Cohen, 1967).

Patients in whom no cause for infertility can be found may still have subtle endocrinological disorders which might respond favourably to this regime.

Evaluation of endogenous estrogenic status could be easily carried out with simple tests like cytohormonal changes in vaginal smears or cervical mucus Fern tests. These tests could thus help in the selection of patients, for the type of therapy and for prognosticating the outcome.

Varied dosage schedules have been used and described in the literature. In our experience, 50 mg daily for 5 days seemed to give the best results though it could not be substantiated statistically. The dosage may be increased to 100 or 200 mg daily if the initial regime failed to induce ovulation in 2 or 3 successive cycles or if the preovulatory phase was too prolonged. Higher dosage would also be indicated if the luteal phase was short.

In most cases the response of an individual to a fixed dosage schedule in successive treatment cycles did not show much variation.

Thus it became important to monitor ovulation time with more sensitive laboratory parameters like daily urinary estrogens and plasma FSH and LH peaks during the post-Clomid period in the initial or early cycles. This was done to assess the temporal relationships of the more simple tests like basal temperature dip, maximum cervical mucus response and karyopyknotic index peak of vaginal smears to more precise tests like estrogenic and LH peaks for timing ovulation in individual cases, so that later on one could with more surety depend on the simpler parameters for assessing the most fertile period for conception.

Our results indicated (Table VI) that the cytohormonal changes in the vaginal smears during the post-clomid phase did not reflect the true estrogenic status or ovulation time when compared to cervical mucus changes, BBT or urinary estrone levels. In most cases the vaginal smears showed such a mass of cytolysis that it was difficult to assess them. In most cases the KPI was low in the preovulatory phase and serial smears rarely showed a

mid-cyclic peak. This unpredictable behaviour of vaginal smears following clomid is probably due to difference in end organ response to the two isomers of clomiphene.

With the 50 mg (50 mg × 5 days) dose schedule the ovulation time as reflected by LH peak and estrogen peaks seemed to occur with a higher probability on post-clomid D_5-D_6 (Jones and Moraes-Ruehsen, 1967). With this information in individual subjects, one could time insemination, natural or artificial, more precisely.

The increase in the post-ovulatory or luteal phase noted after clomid therapy raises interesting speculations. It could be due to the stimulatory action of the drug at the hypothalamic levels causing increased Gn-RH and LH surge, though our results did not indicate higher than normal LH values.

The possibility of early abortion in such cycles also have to be kept in mind. As such there was a high abortion rate 27.2% (15 out of 54 pregnancies) in our study.

In this connection, it would be relevant to point out the higher discrepancy between percentage of ovulatory cycles 81.3% to conception cycles (27.4%) with clomid therapy (Whitelaw *et al*, 1970). It is possible that there may be a failure of implantation or early rejection of an implanted ovum in such cases.

These cases might benefit from a combination of Clomid + HCG therapy (Kistner, 1966) and can be diagnosed early with recent improvements in early pregnancy diagnosis by radioreceptor assay or B-subunit radioimmunoassay.

The question of trapped ovum in a follicle which shows luteinization and all other signs of luteal activity must also be kept in mind (Kase *et al*, 1967).

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