A COMPARATIVE EVALUATION OF CENTCHROMAN AND CLOMIPHENE CITRATE FOR THE INDUCTION OF OVULATION IN INFERTILE WOMEN

A MULTICENTRE PROJECT

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Introduction

Centchroman, 3, 4, trans-2, 2-dimethyl-3-phenyl 4 (P-/B Pyrrolidinoethoxy-phenyl) 7 methoxy chroman (Fig. 1), a synthetic non-steroidal antiestrogenic compound was shown to stimulate the hypothalamo-pituitary gonadotroph axis in healthy male volunteers when a dose of 120 mg/day was given for 7 days (Vaidya *et al* 1976). In similar studies with male rodents an increase in FSH levels in serum as well as in pituitary was also observed in centchroman treated animals (Arbatti *et al* 1977). In another study done in female volunteers, increased levels of oestrogen in treatment cycles were attributed secondary to stimulation of pituitary gonadotropin synthesis, storage and release (Vaidya *et al* 1977). Gonadotropin stimulating property of centchroman was further explored for induction of ovulation in a preliminary study where ovulation was successfully induced in two patients of anovulatory infertility at the Endocrine and Infertility clinic of I.R.R. Roy *et al* (1976) also showed successful induction of ovulation in 4 out of 8 anovulatory women. Hence, it was thought appropriate to compare the relative efficacy of

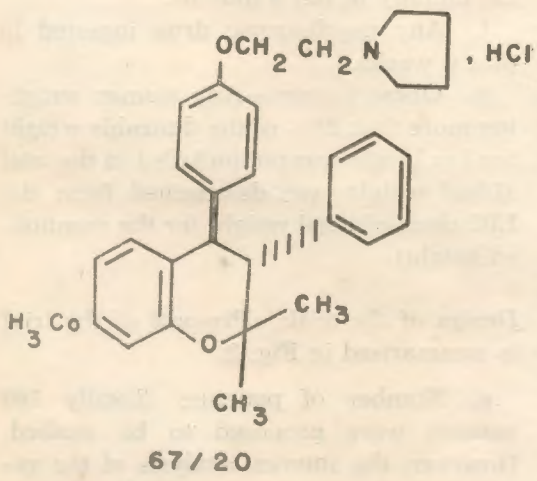

Fig. 1

centchroman with the standard antiestrogen used for the induction of ovulation viz. clomiphene citrate in a group of well-selected infertile patients by randomly allocating the above two drugs according to a predetermined chart.

In the present communication we wish to report the results of this multicentre trial.

Material and Methods

A total of 68 cases having oligomenorrhea or secondary amenorrhea were selected for the trial. These women belonged to group II of WHO classification for selection of patients for therapy of endocrine forms of infertility. This group is suitable for treatment with antiestrogenic drugs like clomiphene citrate (Smith *et al* 1963) and Tamoxifen (Gerhard and Runnebaum 1979). According to this classification of WHO, women belonging to group II have a variety of menstrual disturbances with distinct evidence of ovarian oestrogen production and non-elevated prolactin or gonadotrophin levels. However patients belonging to the same group but having regular or irregular anovulatory cycles (< 60 days) and those with luteal phase defects were not included in the trial. Patients of oligomenorrhea with cycle length of more than 60 days and those having secondary amenorrhea with positive response to progesterone challenge test were considered suitable for the trial. Progesterone challenge test was used along with comprehensive history taking, physical and gynaecological examination for initial screening and selection of the patients. This clinical approach was to a large extent successful and excluded the other groups of WHO classification who are not suitable for therapy with antiestrogens. Subsequent estimations of serum Follicular Stimulating Hormone (FSH) however showed consistent increase of serum FSH in four who were excluded from the trial. Other six patients dropped out at the very initiation of trial for various reasons unrelated to drug therapy. Thus a total of 58 cases participated in the trial. Serum prolactin was found to be mildly elevated (> 20 ng/ml, < 40 ng/ml) in 4 patients, 2 each from clomiphene citrate and centchroman therapy groups.

Criteria for exclusion

a. Regularly menstruating women with anovulatory cycles of less than 60 days or those with luteal phase defect.

b. Those with tubal pathology. A diagnostic laparoscopy was performed on these patients selected for trial in order to rule out pelvic pathology and/or tubal lesions.

c. Women who had a wedge resection done for polycystic ovaries or any other ovarian surgery in the past.

d. Those who were given ovulation inducing agents in previous 3 months.

e. Those who had taken O.C. or cyclical therapy in last 3 months.

f. Any psychotropic drug ingested in past 6 weeks.

g. Obese women—Any woman weighing more than 20% of the desirable weight for her height was not included in the trial (Ideal weight was determined from the LIC chart of ideal weight for the mentioned height).

Design of the trial: Protocol of the trial is summarised in Fig. 2.

a. Number of patients: Totally 100 patients were proposed to be studied. However, the interim analysis of the results of the trial prompted earlier termination.

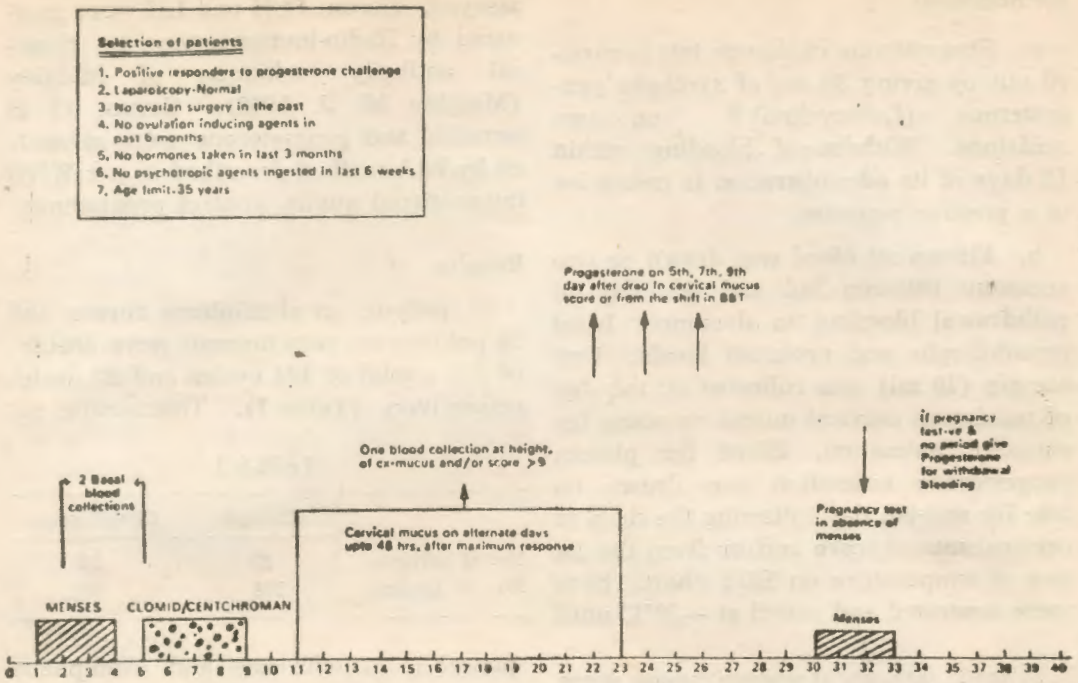

Fig. 2

b. Dose schedule: Drugs were allocated according to the predesigned random chart. Patients followed the regime as shown in the flow chart. Each drug was started on the 5th day of the induced menstrual period and continued for 5 days. A higher dose schedule was utilized when ovulation failed to occur with a lower dose of the drug given for 2 consecutive cycles.

Monitoring of therapeutic responses and side effects

Monitoring of therapeutic responses which included occurrence of ovulation was done during the trial by

1. Basal body temperature recording.
2. Cervical mucus scoring: Cervical mucus was watched from 48 hours following last pill and continued on alternate days until a maximum mucus response was reached and continued for 48 hours thereafter. Cervical mucus scoring was done according to modified WHO scoring system.

3. Serum progesterone estimations were done to document ovulation. A value of 5 ng/ml was considered indicative of ovulation. When cycle length was $>$ 40 days during therapy a pregnancy test was performed and if negative the next course of drug was started from the 5th day of subsequent induced period.

Throughout the trial patients were monitored for the possible side effects such as vasomotor flushes, abdominal pain/distension, vomiting, visual symptoms, headache and loss of hair. Follow up pelvic examinations were done every cycle so as to detect undue enlargement of ovaries due to hyperstimulation.

Methodology

a. Progesterone challenge test is carried out by giving 50 mg of synthetic progesterone (Lutocycline)® on two occasions. Withdrawal bleeding within 15 days of its administration is indicative of a positive response.

b. Fifteen ml blood was drawn on two occasions between 2nd and 5th day of withdrawal bleeding to document basal gonadotropin and prolactin levels. One sample (10 ml) was collected on the day of maximum cervical mucus response for estradiol estimation. Blood for plasma progesterone estimation was drawn on 5th, 7th and 9th day following the drop in cervical mucus score and/or from the 1st rise of temperature on BBT chart. Sera were separated and stored at —20°C until assayed. Serum FSH and LH were measured by Radio-immunoassay by classical antibody technique of Midgley (Midgley M. J. 1966). Serum 17 B estradiol and progesterone were measured by RIA method described as per WHO international quality control programme.

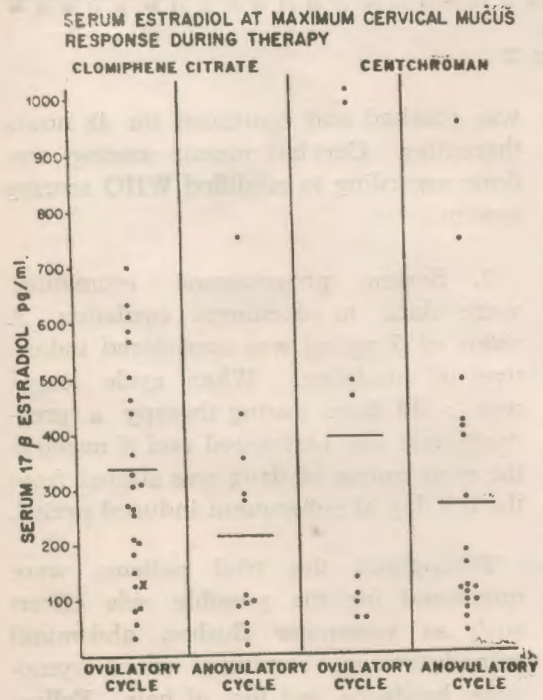

Fig. 3

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Results

33 patients on clomiphene citrate and 25 patients on centchroman were observed for a total of 104 cycles and 82 cycles respectively (Table I). Therapeutic responses to centchroman and clomiphene citrate are shown in Table II. 30 patients ovulated on clomiphene citrate giving a success rate of 91% for ovulation. However the ovulatory responses were not uniform throughout the treatment period. Only 62% of treatment cycles were ovulatory (65/104 cycles). 15 of the 30 responding patients on clomiphene citrate conceived and 10 delivered normal babies. One of these had a twin pregnancy. The remaining 5 patients aborted. The therapeutic responses in terms of ovulation and

TABLE I

	Clomid	Centchroman
No. of patients	33	25
No. of cycles	104	82

TABLE II

Therapeutic Response during Clomiphene Citrate and Centchroman Treatment

	Clomiphene citrate		Centchroman	
	No.	%	No.	%
A *Ovulation*				
No. of patients	30	91	12	48
No. of cycles	65	62	19	23
B *Pregnancies*	15	45	1	4

pregnancy were consistently poor in women treated with centchroman. Only 19 of the treated cycles were ovulatory inspite of 48% of patients showing occasional ovulation. There was only one pregnancy in the group.

Table III shows menstrual pattern during drug therapy. Episodes of menstrual bleeding within 40 days of clomid therapy was observed in 65 therapy cycles while only 31 cycles on centchroman therapy showed such a pattern. Menstruation was induced by progesterone administration whenever the therapy cycles were prolonged more than 40 days in the absence of pregnancy. Progesterone ad ministration was required during 20 cycles of clomid therapy and 31 cycles of centchroman therapy. It was interesting to note that progesterone administration brought about withdrawal bleeding in all the 29 cycles of clomid therapy, while 6 cycles during centchroman therapy could not be induced by progesterone alone and a combination estrogen and progesterone was required to initiate therapy for the fresh cycle. The Fig. 3 depicts the serum 17 B estradiol levels during clomid and centchroman therapy in ovulatory and anovulatory cycles. It was of interest to observe that several women on clomid and centchroman therapy had elevated estradiol values (300 pg/ml-1000 pg/ml) indicative of follicular growth inspite of anovulation.

TABLE III
Menstrual Pattern during Clomiphene Citrate and Centchroman Treatment

	Clomiphene citrate	Centchroman
Spontaneous menstruation	65 cycles	31 cycles
Progesterone withdrawal positive	20 cycles	38 cycles
Progesterone withdrawal negative	—	6 cycles
Conception cycles	15 cycles	1 cycle
Not known	4 cycles	6 cycles

Side effects: Except for palpably enlarged and tender ovaries in two patients on centchroman therapy no other serious side effects were observed in women on either of the drug therapies.

Discussion

In the present study the incidence of ovulation and pregnancy on centchroman are compared with the standard antiestrogenic drug viz. clomiphene citrate. The dose of 60 mgm and 120 mgm for centchroman was chosen from the experience of the previous studies where an increase in serum FSH/LH and 24 hours urinary LH indicative of stimulation of pituitary gonadotropin was shown (Vaidya *et al* 1976).

Progesterone challenge test was utilized for initial screening and selection of patients. It is shown that patients of secondary amenorrhea will respond to antiestrogens only if they have some degree of endogenous estrogen production. A progesterone induced withdrawal bleeding indirectly implies priming of endometrium by endogenous estrogen (Shringi *et al* 1981). In a study conducted at IRR, 7.4% of responders to progesterone challenge test were found to have premature ovarian failure as diagnosed by consistently elevated levels of serum FSH (Meherji *et al* 1980). Mild hyperprolactinemia was detected in 6% of cases. In the present study too, 4 women were found to have mild hyperprolactinemia and two of them ovulated and conceived. Fortunately they were equally distributed in both the drug groups. Women with mild degree of hyperprolactinemia are

known to have withdrawal bleeding on progesterone administration as well as ovulation on clomiphene citrate therapy (March *et al* 1979). Progesterone challenge test will therefore rule out most of the cases of premature ovarian failure as well as those with severe degree of hyperprolactinemia.

The incidence of ovulation and pregnancy with clomiphene citrate therapy has ranged from 50% to 90% and 11% to 45% respectively in various series (Table IV.) Our result of 91% ovulation rate and 45% pregnancy rate compares well with those reported in the literature.

TABLE IV

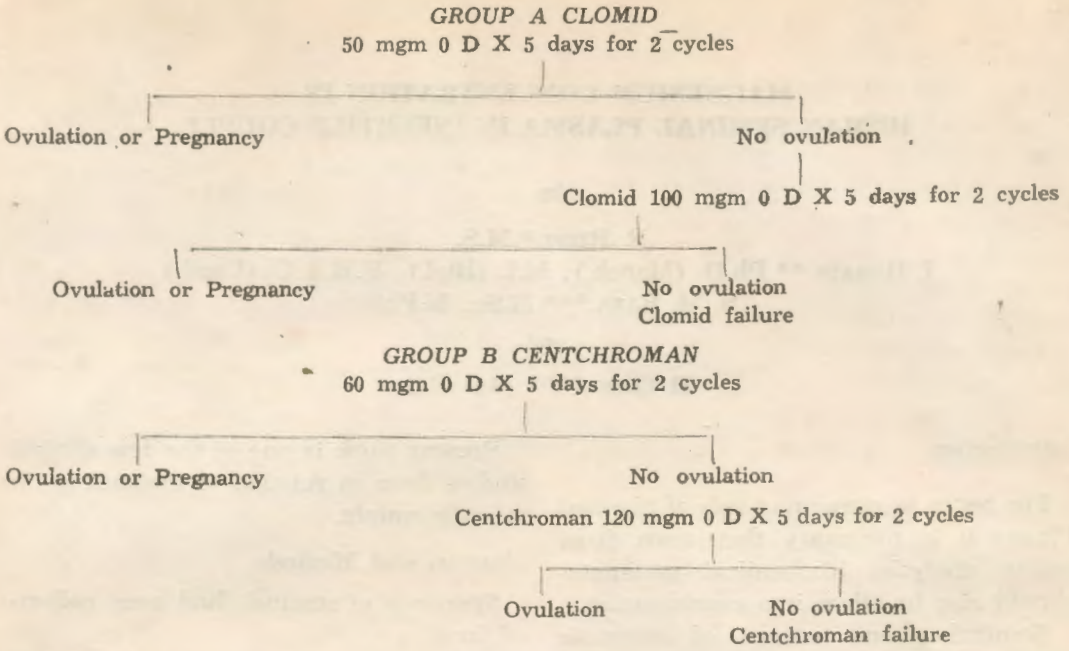
Ovulation and Pregnancy Rates Following Clomiphene Citrate Therapy

Authors	Patients No.	Ovulation %	Pregnancy %
Seegar-Jones and Moraes-Ruehsen (1967)	73	83.0	30.1
Macgregor *et al* (1968)	6714	70.0	32.7
Whitelaw *et al* (1970)	37	72.9	45.9
Kistner (1975)	2616	69.2	28.4
Present series	30	91	45

The incidence of ovulation during centchroman therapy was poor compared to that observed during clomiphene citrate therapy. Though 45% of patients showed occasional ovulation, the response was inconsistent and only 23% of cycles were ovulatory. Similarly, the conception rate was also poor on centchroman. Only one patient conceived during centchroman therapy giving 4% pregnancy rate as compared to 45% pregnancy rate in patients on clomiphene citrate therapy.

In other series by Roy *et al* (1976) and Maewal *et al* (1980), the ovulation during centchroman therapy is reported in 50% and 65% of patients respectively. The dose used by Maewal *et al* was similar to that used in the present study. Since Maewal *et al* have observed 20 patients only for one and in occasional patients for two cycles during centchroman therapy it is difficult to predict how many of their patients would consistently ovulate in the subsequent cycles. The failure of progesterone administration to induce withdrawal bleeding in prolonged cycles during centchroman therapy may indicate a profound anti-estrogenic activity at the target organ viz. endometrium. A similar prolonged retention of antiestrogenic activity at hypothalamo pituitary level may explain the failure of ovulation inspite of high circulating estradiol levels. An unusually prolonged occupancy of hypothalamic steroidal receptors may interfere with positive feedback mechanism essential for preovulatory LH surge.

It is concluded from the present study that centchroman at the tried out doses and schedule (60 mgm/day and 120 mgm/day for 5 days) does not provide an effective agent for induction of ovulation for the specific group of patients with secondary amenorrhea and anovulatory infertility. It also compares poorly with reference to antiestrogenic agents viz. clomiphene citrate for the mentioned indication viz. induction of ovulation.



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